10/066,965

```
=> d his

     (FILE 'REGISTRY' ENTERED AT 07:06:48 ON 26 OCT 2004)
                DEL HIS

     FILE 'HCAPLUS' ENTERED AT 07:08:27 ON 26 OCT 2004
L1            1 S US20030143626/PN OR (EP2000-403156 OR US2001-066965#)/AP,PRN
                E COLAS P/AU
L2          164 S E3,E5
                E BRENT R/AU
L3          110 S E3-E6,E14,E15
                E COHEN B/AU
L4           84 S E3-E5
L5           10 S E21-E23
L6         2699 S INTRACELL? (L) RECOGN? (L) (MOLECUL? OR DOMAIN OR MOIET?)
L7         5267 S INTRACELL? (L) TARGET? (L) (MOLECUL? OR DOMAIN OR MOIET?)
L8          523 S L6 AND L7
L9           41 S L8 AND CONFORM?
L10          23 S L8 AND COVALENT?
L11          58 S L8 AND (MUTAT? OR MUTAG?)
L12          27 S L8 AND ?DIMER?
L13          62 S L8 AND ?LINK?
L14           0 S L8 AND ?PLATFORM?
L15          10 S L8 AND HETEROLOG?
L16         446 S L8 AND (?PROTEIN? OR ?PEPTIDE?)
L17         156 S L16 AND L9-L15
L18           2 S L8 AND ?THIOREDOXIN?
L19           0 S L8 AND TRX
                E THIOREDOXIN/CT
L20        2838 S E9-E15
                E E9+ALL
L21        2860 S E3,E2,E5
L22           2 S L8 AND L20-L21
L23        5251 S L20,L21 OR ?THIOREDOXIN? OR ?THIO REDOXIN? OR TRX
L24       15357 S CDK2 OR CD K2 OR CDK 2 OR CYCLIN DEPENDENT KINASE 2 OR CYCLIN
L25        6645 S PROAPOPTO? OR PRO(L)APOPTO?
L26          84 S L23 AND L24,L25

     FILE 'REGISTRY' ENTERED AT 07:26:47 ON 26 OCT 2004
                E CYCLIN/CN
                E CYCLIN-DEPENDENT/CN
L27           4 S E4,E10,E15,E23
L28           2 S E33,E34
L29           2 S E37,E40
L30         485 S CYCLIN DEPENDENT KINASE

     FILE 'HCAPLUS' ENTERED AT 07:28:20 ON 26 OCT 2004
L31        5271 S L27-L29
L32        7744 S L30
L33          43 S L23 AND L31,L32
L34          93 S L26,L33
L35          20 S L34 AND ?INTRACELL?

     FILE 'REGISTRY' ENTERED AT 07:29:32 ON 26 OCT 2004
                E THIOREDOXIN
L36        2125 S E3-E8

     FILE 'HCAPLUS' ENTERED AT 07:29:43 ON 26 OCT 2004
L37        1983 S L36
L38         146 S L37,L23 AND L24,L25,L31,L32
L39          21 S L38 AND ?INTRACELL?
L40           4 S L38 AND TARGET? AND RECOGN?
L41           8 S L38 AND CONFORM?
```

```
L42          26 S L39-L41,L18,L22
L43           1 S L17 AND L42
L44           1 S L17 AND L38
L45      158240 S PROTEIN#/CW (L) PROC+NT/RL
L46           8 S L45 AND L38
L47       11229 S L45 AND CONFORM?
L48          45 S L47 AND REACTION KINETIC?/CT
                E REACTION KINETICS/CT
L49         357 S L2-L5
L50           1 S L49 AND L8
L51           6 S L49 AND L38
L52          29 S L1,L42-L44,L46,L50,L51
L53           1 S L48 AND L52
                E BOND/CT
L54        2263 S E31
                E E3+ALL
L55      708009 S E2+OLD,NT,PFT,RT
L56        3325 S E2-E4 (L) COVALEN?
L57          10 S L55,L56 AND L38
L58          40 S L55,L56 AND L8
L59          73 S L57,L58,L52,L53
L60          14 S L25 AND L59
L61          18 S L59 AND CONFORM?
L62          23 S L45 AND L59
L63          61 S L59 AND ?INTRACELL?
L64          21 S L63 AND L38
L65           6 S L59 AND L1-L5
L66          67 S L59 NOT L65
                SEL DN AN 10 15 29 59 L66
L67           4 S L66 AND E1-E12
                E PROTEIN MOTIF/CT
                E E4+ALL
L68       56145 S E4+NT
L69          12 S L68 AND L38
L70          65 S L68 AND L8
L71          55 S L69,L70 NOT L65,L66
                SEL DN AN 52 55
L72           2 S E1-E6 AND L71
                E CONFORMATION/CT
                E E3+ALL
L73      541662 S E2+OLD,NT,PFT,RT
L74       11075 S L68 AND L73
L75          22 S L74 AND REACTION KINETIC?/CT
L76           3 S L74 AND L38
L77           2 S L76 NOT IMMUNOTOXIN/TI
L78          12 S L65,L67,L72,L77
L79          12 S L78 AND L1-L26,L31-L35,L37-L78

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 07:56:03 ON 26 OCT 2004
```

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

Copyright of the articles to which records in this database refer is held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications. The CA Lexicon is the copyrighted intellectual property of the the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS, is

strictly prohibited.

FILE COVERS 1907 - 26 Oct 2004 VOL 141 ISS 18
FILE LAST UPDATED: 25 Oct 2004 (20041025/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d l79 all tot

L79 ANSWER 1 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **2004:44221** HCAPLUS
DN **140:178592**
ED Entered STN: 19 Jan 2004
TI Redox regulation of cell growth and death by **thioredoxin** family
AU Oka, S.; Ahsan, Md. K.; Nishinaka, Y.; Tanaka, T.; Matsuo, Y.; Masutani, H.; Nakamura, H.; Yodoi, J.
CS Biomedical Special Research Unit, Human Stress Signal Research Center, National Institute of Advanced Industrial Science and Technology, Midorigaoka, Ikeda, Osaka, Japan
SO Proceedings of [the] Biennial Meeting of the Society for Free Radical Research International, 11th, Paris, France, July 16-20, 2002 (2002), 259-263. Editor(s): Pasquier, Catherine. Publisher: Monduzzi Editore, Bologna, Italy.
CODEN: 69EZI4; ISBN: 88-323-2716-3
DT Conference; General Review
LA English
CC 13-0 (Mammalian Biochemistry)
AB A review. Recent studies have shown the importance of reduction/oxidation (redox) regulation in various biol. phenomena. **Thioredoxin** (**TRX**) is a 12-kDa protein with redox active dithiol in the active site -Cys-Gly-**Pro**-Cys- and is key component of a major reducing system, the **thioredoxin** system. **Thioredoxin** plays multiple regulatory roles in cellular processes such as proliferation or **apoptosis** through regulation of cellular signaling mols. including NF-.vkappa.B, AP-1 and p53. **Thioredoxin** acts not simply as a scavenger of reactive oxygen species (ROS) but also as an important regulator of oxidative stress response by protein-protein interaction. We recently identified **TRX**-binding protein-2 (TBP-2) as a neg. regulator of **TRX.** We showed that members of **TRX** superfamily with conserved **TRX** like redox-active site, play an important role in biol. responses. **Thioredoxin**-related transmembrane protein (TMX) is identified as a TGFβ-inducible gene, which prevents ER stress-induced **apoptosis. Thioredoxin** -2 (**TRX**-2) is a mitochondria-specific member of the family. **Trx**-2 deficient cells undergo **apoptosis** in association with accumulation of **intracellular** ROS. Thus, **TRX**-2 has a crucial role in cell survival.
ST review **thioredoxin** redox regulation cell growth apoptosis oxidative stress
IT **Thioredoxins**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(**2**; redox regulation of cell growth and death by **thioredoxin** family)
IT Proteins
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(TBP-2 (**thioredoxin**-binding protein-2); redox regulation of cell growth and death by **thioredoxin** family)
IT Reduction
(biol.; redox regulation of cell growth and death by

thioredoxin family)
IT Apoptosis
Cell death
Cell proliferation
Oxidative stress, biological
(redox regulation of cell growth and death by **thioredoxin** family)
IT **Thioredoxins**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(redox regulation of cell growth and death by **thioredoxin** family)
IT Proteins
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(transmembrane, TMX (**thioredoxin**-related transmembrane protein); redox regulation of cell growth and death by **thioredoxin** family)
RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE

(1) Bodnar, J; Nat Genet 2002, V30, P110 HCAPLUS
(2) Butler, L; Proc Natl Acad Sci U S A 2002, V99, P11700 HCAPLUS
(3) Chen, K; Biochim Biophys Acta 1994, V1219, P26 HCAPLUS
(4) Chen, Y; J Biol Chem 2002, V277, P33242 HCAPLUS
(5) Damdimopoulos, A; J Biol Chem 2002, V277, P33249 HCAPLUS
(6) Hirota, K; J Biol Chem 1999, V274, P27891 HCAPLUS
(7) Holmgren, A; Annu Rev Biochem 1985, V54, P237 MEDLINE
(8) Joguchi, A; Biochem Biophys Res Commun 2002, V293, P293 HCAPLUS
(9) Junn, E; J Immunol 2000, V164, P6287 HCAPLUS
(10) Kamata, H; Cell Signal 1999, V11, P1 HCAPLUS
(11) Masutani, H; Methods Enzymol 2002, V347, P279 HCAPLUS
(12) Matsuo, Y; J Biol Chem 2001, V276, P10032 HCAPLUS
(13) Nishiyama, A; J Biol Chem 1999, V274, P21645 HCAPLUS
(14) Nishiyama, A; Submitted
(15) Saitoh, M; Embo J 1998, V17, P2596 HCAPLUS
(16) Saitoh, T; J Neurochem 2001, V78, P1267 HCAPLUS
(17) Spyrou, G; J Biol Chem 1997, V272, P2936 HCAPLUS
(18) Suzuki, T; Exp Gerontol 2001, V36, P465 HCAPLUS
(19) Tagaya, Y; Embo J 1989, V8, P757 HCAPLUS
(20) Tanaka, T; Embo J 2002, V21, P1695 HCAPLUS
(21) Yamanaka, H; Biochem Biophys Res Commun 2000, V271, P796 HCAPLUS

L79 ANSWER 2 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **2003:705542** HCAPLUS
DN **139:390903**
ED Entered STN: 09 Sep 2003
TI A novel organoselenium compound induces cell cycle arrest and apoptosis in prostate cancer cell lines
AU Shi, Changjin; Yu, Lizhang; Yang, Fengguang; Yan, Jun; Zeng, Huihui
CS Institute of Urology, Department of Molecular Biology, First Hospital, Peking University, Beijing, 100034, Peop. Rep. China
SO Biochemical and Biophysical Research Communications (2003), 309(3), 578-583
CODEN: BBRCA9; ISSN: 0006-291X
PB Elsevier Science
DT Journal
LA English
CC 1-6 (Pharmacology)
Section cross-reference(s): 7, 29
AB **Thioredoxin** reductase (TrxR) in conjunction with **thioredoxin** (**Trx**) is a ubiquitous **intracellular** oxidoreductase system with antioxidant and redox regulatory roles. The properties of TrxR in combination with the functions of **Trx**

position this system at the core of cellular thiol redox control and antioxidant defense. In some human tumors, the **thioredoxin** system is found over-expressed. Because of its role in stimulating cancer cell growth and as an inhibitor of apoptosis, the **Trx** system offers a **target** for the development of drugs to treat and prevent cancer. In a previous research, we successfully synthesized a novel organoselenium compound BBSKE(1,2-[bis(1,2-Benzisoselenazolone-3(2H)-ketone)]ethane, BBSKE, PCT: CN02/00412) **targeting** the TrxR, and it has demonstrated the inhibitory effect on the growth of a variety of human cancer cells from various organs. In this study, we investigated the inhibitory effect of BBSKE on TrxR activity in PC-3 and DU145 human prostate cancer cell lines, and its antitumoral effect on these two cell lines. Treatment of BBSKE inhibited the TrxR activity in both of the cell lines in a dose-dependent manner and it also inhibited the proliferation of these two cell lines in a dose-dependent manner. Cell cycle anal. showed S phase arrest in both of the cell lines following 48 h exposure to BBSKE. During the S arrest, anal. of cell cycle regulatory proteins demonstrated that BBSKE increased the protein levels of cyclinA, cyclinE, and P21, but decreased the levels of cyclinB1, cyclinD1, and Cdk4. Furthermore, BBSKE decreased the protein level of Bcl-2 but increased the level of Bax, and induced apoptosis in PC-3 and DU145 human prostate cancer cell lines. These results suggest that this novel TrxR inhibitor inhibits the proliferation of prostate cancer cells via S phase arrest and apoptosis in association with the regulation of multiple **mols.** in the cell cycle.

ST organoselenium antitumor apoptosis prostate cancer cyclin cdk Bcl2 Bax; benzisoselenazolone ketone ethane BBSKE **thioredoxin** inhibitor cell cycle block

IT Cyclins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(A; novel organoselenium compound induces cell cycle arrest and apoptosis in prostate cancer cell)

IT Cyclins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(B1; novel organoselenium compound induces cell cycle arrest and apoptosis in prostate cancer cell)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Bax; novel organoselenium compound induces cell cycle arrest and apoptosis in prostate cancer cell)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Bcl-2; novel organoselenium compound induces cell cycle arrest and apoptosis in prostate cancer cell)

IT Cyclins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(D1; novel organoselenium compound induces cell cycle arrest and apoptosis in prostate cancer cell)

IT Cyclins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(E; novel organoselenium compound induces cell cycle arrest and apoptosis in prostate cancer cell)

IT Interphase (cell cycle)
(S-phase; novel organoselenium compound induces cell cycle arrest and apoptosis in prostate cancer cell)

IT Antitumor agents
Apoptosis
Cell cycle
Cytotoxic agents
Human
Prostate gland, neoplasm
(novel organoselenium compound induces cell cycle arrest and apoptosis in prostate cancer cell)

IT Organometallic compounds
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel organoselenium compound induces cell cycle arrest and apoptosis in prostate cancer cell)

IT **Cyclin dependent kinase** inhibitors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p21CIP1; novel organoselenium compound induces cell cycle arrest and apoptosis in prostate cancer cell)

IT **9074-14-0**, **Thioredoxin** reductase **147014-97-9**, Cdk4 kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(novel organoselenium compound induces cell cycle arrest and apoptosis in prostate cancer cell)

IT 217798-39-5
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel organoselenium compound induces cell cycle arrest and apoptosis in prostate cancer cell)

RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE
(1) Ahmad, N; Biochem Biophys Res Commun 2000, V275, P328 HCAPLUS
(2) Berggren, M; Anticancer Res 1996, V16, P3459 HCAPLUS
(3) Deng, S; J Peking Univ (Health Sciences) 2003, V35, P108 HCAPLUS
(4) Dulic, V; Science 1992, V257, P1958 HCAPLUS
(5) El-Deiry, W; Cell 1993, V75, P817 HCAPLUS
(6) Galter, D; Eur J Biochem 1994, V221, P639 HCAPLUS
(7) Gasdaska, J; Cell Growth Differ 1995, V6, P1642
(8) Gasdaska, P; Biochim Biophys Acta 1994, V1218, P292 HCAPLUS
(9) Greenlee, R; CA Cancer J Clin 2001, V51, P15 MEDLINE
(10) Harper, J; Cell 1993, V75, P805 HCAPLUS
(11) Hill, K; Biochem Biophys Res Commun 1997, V234, P293 MEDLINE
(12) Holmgren, A; Annu Rev Biochem 1985, V54, P237 MEDLINE
(13) Huang, P; Cancer Res 1997, V57, P3407 HCAPLUS
(14) Laurent, T; J Biol Chem 1964, V239, P3436 HCAPLUS
(15) Matthews, J; Nucleic Acids Res 1992, V20, P3821 HCAPLUS
(16) Mohler, J; Prostate 2002, V51, P247 HCAPLUS
(17) Nakamura, H; Cancer 1992, V69, P2091 HCAPLUS
(18) Powis, G; Anticancer Drugs 1996, V7(Suppl 3), P121
(19) Rini, B; Curr Opin Oncol 2002, V14, P286
(20) Salomons, G; Int J Cancer 1997, V71, P959 HCAPLUS
(21) Sedlak, T; Proc Natl Acad Sci USA 1995, V92, P7834 HCAPLUS
(22) Sherr, C; Cancer Res 2000, V60, P3689 HCAPLUS
(23) Sherr, C; Cell 1993, V73, P1059 HCAPLUS
(24) Sherr, C; Science 1996, V274, P1672 HCAPLUS
(25) Xiong, Y; Nature 1993, V366, P701 HCAPLUS
(26) Yokomizo, A; Caner Res 1995, V55, P293

L79 ANSWER 3 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:425354 HCAPLUS
DN 137:2729
ED Entered STN: 06 Jun 2002
TI Interaction trap systems for detecting protein interactions
IN **Brent, Roger**; McCoy, John M.; Jessen, Timm H.; Xu, Chanxing Wilson
PA The General Hospital Corporation, USA
SO U.S., 30 pp., Cont.-in-part of U. S. 6,004,746.
CODEN: USXXAM
DT Patent
LA English
IC ICM C12Q001-68
ICS G01N033-53
NCL 435006000

CC 9-2 (Biochemical Methods)
Section cross-reference(s): 3, 6

FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6399296	B1	20020604	US 1996-630052	19960409
	US 6004746	A	19991221	US 1995-504538	19950720
	EP 1405911	A1	20040407	EP 2003-21647	19950720
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE				
	WO 9738127	A1	19971016	WO 1997-US5793	19970409
	W: JP				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	EP 904402	A1	19990331	EP 1997-917897	19970409
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
	JP 2000508174	T2	20000704	JP 1997-536441	19970409
	US 2003113749	A1	20030619	US 2002-162538	20020604
PRAI	US 1994-278082	A2	19940720		
	US 1995-504538	A2	19950720		
	EP 1995-928118	A3	19950720		
	US 1996-630052	A	19960409		
	WO 1997-US5793	W	19970409		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 6399296	ICM	C12Q001-68
	ICS	G01N033-53
	NCL	435006000
US 6399296	ECLA	C12N009/02D; C12N015/10C6; C12Q001/68P
WO 9738127	ECLA	C12N009/02D; C12Q001/02B; C12Q001/68P
US 2003113749	ECLA	C12N009/02D; C12N015/10C6; C12Q001/02B; C12Q001/68P

AB Disclosed herein is a method of determining whether a first protein is capable of phys. interacting with a second protein, involving: (a) providing a host cell which contains (i) a reporter gene operably linked to a protein binding site; (ii) a first fusion gene which expresses a first fusion protein, the first fusion protein including the first protein covalently bonded to a binding moiety which is capable of specifically binding to the protein binding site; and (iii) a second fusion gene which expresses a second fusion protein, the second fusion protein including the second protein covalently bonded to a gene activating moiety and being **conformationally**-constrained; and (b) measuring expression of the reporter gene as a measure of an interaction between the first and the second proteins. Also disclosed are methods for assaying protein interactions, and identifying antagonists and agonists of protein interactions. A **thioredoxin** interaction trap system was used with **Cdk2** as bait in a yeast two-hybrid system to screen for interacting peptides. Growth on leucine-deficient medium was used in the first selection step. The largest colonies were streak purified and tested for the galactose-dependent expression of the LEU2 gene product and of β-galactosidase. The strength of peptide binding to bait was judged according to the intensity of the blue color produced by β-galactosidase.

ST trap system detecting protein interaction; **thioredoxin** trap **Cdk2** bait peptide binding assay

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CDC28; interaction trap systems for detecting protein interactions)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Cdc2; interaction trap systems for detecting protein interactions)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Cdc2c; interaction trap systems for detecting protein interactions)

IT Proteins

RL: ARG (Analytical reagent use); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(DNA-binding, reporter gene operably linked to recognition site for; interaction trap systems for detecting protein interactions)

IT Cyclins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(E, complexes, with **Cdk2** kinase; interaction trap systems for detecting protein interactions)

IT Proteins
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(H-ras; interaction trap systems for detecting protein interactions)

IT Histones
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(H1; interaction trap systems for detecting protein interactions)

IT Signal peptides
(NLS (nuclear localization signal), prey vector encoding fusion protein containing, of SV40; interaction trap systems for detecting protein interactions)

IT Genetic element
RL: ARG (Analytical reagent use); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(activating; interaction trap systems for detecting protein interactions)

IT Transcriptional regulation
(activation, prey vector encoding fusion protein containing B112 domain for; interaction trap systems for detecting protein interactions)

IT Enzyme functional sites
(active, loop of **thioredoxin**, protein insertion into; interaction trap systems for detecting protein interactions)

IT **Thioredoxins**
RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(as **conformation**-constraining protein, fusion proteins; interaction trap systems for detecting protein interactions)

IT Gene, animal
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(c-Ha-ras; interaction trap systems for detecting protein interactions)

IT Gene, animal
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(**cdk2**; interaction trap systems for detecting protein interactions)

IT Proteins
RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**conformation**-constraining, fusion proteins; interaction trap systems for detecting protein interactions)

IT Proteins
RL: ARG (Analytical reagent use); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(conjugates, with DNA-binding protein; interaction trap systems for detecting protein interactions)

IT Phosphoproteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene **cdk2**, complexes, with cyclin E kinase; interaction trap systems for detecting protein interactions)

IT Immunoassay
(immunoblotting; interaction trap systems for detecting protein interactions)

IT Immunoassay
(immunopptn.; interaction trap systems for detecting protein interactions)
IT Affinity chromatography
Cell
Escherichia coli
Human
Molecular association
Peptide library
Protein motifs
(interaction trap systems for detecting protein interactions)
IT Peptides, analysis
Proteins
RL: ANT (Analyte); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PREP (Preparation)
(interaction trap systems for detecting protein interactions)
IT Reporter gene
RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(interaction trap systems for detecting protein interactions)
IT Chimeric gene
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(interaction trap systems for detecting protein interactions)
IT Fusion proteins (chimeric proteins)
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(interaction trap systems for detecting protein interactions)
IT Gene, microbial
RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(lacZ; interaction trap systems for detecting protein interactions)
IT Gene, microbial
Transcription factors
RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(lexA; interaction trap systems for detecting protein interactions)
IT Simian virus 40
(prey vector encoding fusion protein containing nuclear localization domain of; interaction trap systems for detecting protein interactions)
IT **Conformation**
(protein, constrained; interaction trap systems for detecting protein interactions)
IT Gene, microbial
RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(trxA, prey vector containing; interaction trap systems for detecting protein interactions)
IT Yeast
(two-hybrid system; interaction trap systems for detecting protein interactions)
IT 52-90-4, L-Cysteine, properties
RL: PRP (Properties)
(at N- and C-termini of protein and forming **conformational** constraint; interaction trap systems for detecting protein interactions)
IT 9031-11-2P, β-Galactosidase
RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); ANST

(Analytical study); BIOL (Biological study); PREP (Preparation); USES
(Uses)
(interaction trap systems for detecting protein interactions)
IT **141349-86-2P, Cdk2** kinase
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified);
BIOL (Biological study); PREP (Preparation)
(interaction trap systems for detecting protein interactions)
IT **175799-49-2P 175799-51-6P 175799-52-7P**
175799-53-8P 175799-54-9P 175799-55-0P
175799-56-1P 175799-57-2P 175799-58-3P
175799-59-4P 175923-55-4P 175923-56-5P 175923-57-6P
175923-58-7P 175923-59-8P 252852-68-9P 252852-70-3P 252852-71-4P
432830-86-9P 432830-87-0P 432830-88-1P 432830-89-2P 432837-66-6P
432837-67-7P 432837-68-8P
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified);
PRP (Properties); BIOL (Biological study); PREP (Preparation)
(interaction trap systems for detecting protein interactions)
IT **153190-71-7**, Cdk3 kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(interaction trap systems for detecting protein interactions)
IT 433272-91-4
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL
(Biological study)
(interaction trap systems for detecting protein interactions)
IT 61-90-5, L-Leucine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(medium deficient in, in selection process; interaction trap systems
for detecting protein interactions)
RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Anon; EP 0496162 1992 HCAPLUS
(2) Anon; WO 9410300 1994 HCAPLUS
(3) Chakraborty; J Biol Chem 1992, V267, P17498 HCAPLUS
(4) Chien; PNAS USA 1991, V88, P9578 HCAPLUS
(5) Fields; US 5283173 A 1994 HCAPLUS
(6) Fields; Trends in Genetics 1994, V10, P286 HCAPLUS
(7) Goding; Monoclonal Antibodies:Principles and Practice 1983, P56
(8) Harper; Cell 1993, V75, P805 HCAPLUS
(9) Hartley; Cellular Interactions in Development, A Practical Approach 1994,
P153
(10) McCoy; US 5270181 A 1993 HCAPLUS
(11) Olivera; US 5885780 A 1999 HCAPLUS
(12) Pawson; US 5352660 A 1994 HCAPLUS

L79 ANSWER 4 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:363978 HCAPLUS
DN 136:382539
ED Entered STN: 16 May 2002
TI **Targeted** modification of **intracellular** compounds
IN **Colas, Pierre; Brent, Roger; Cohen, Barak A.**
PA Centre National De La Recherche Scientifique, Fr.; Massachusetts General
Hospital; Molecular Sciences Institute
SO Eur. Pat. Appl., 33 pp.
CODEN: EPXXDW
DT Patent
LA English
IC ICM A61K047-48
CC 9-16 (Biochemical Methods)
Section cross-reference(s): 1, 3, 6
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 1205191	A1	20020515	EP 2000-403156	20001113 <--

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
WO 2002055108 A1 20020718 WO 2001-EP14199 20011113 <--
WO 2002055108 C2 20030515
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,
UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
US 2003143626 A1 20030731 US 2001-66965 20011113 <--
EP 1345627 A1 20030924 EP 2001-273076 20011113 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
JP 2004516848 T2 20040610 JP 2002-555840 20011113 <--
PRAI EP 2000-403156 A 20001113 <--
WO 2001-EP14199 W 20011113
CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES	
EP 1205191	ICM	A61K047-48	
US 2003143626	ECLA	A61K047/48R2H	<--
JP 2004516848	FTERM	2G045/AA40; 2G045/CB01; 2G045/CB21; 2G045/DA12; 2G045/DA13; 2G045/DA14; 2G045/DA20; 2G045/DA36; 2G045/FB02; 2G045/FB03; 4B024/AA01; 4B024/AA11; 4B024/BA80; 4B024/CA01; 4B024/CA07; 4B024/CA11; 4B024/DA01; 4B024/DA02; 4B024/DA05; 4B024/DA11; 4B024/DA12; 4B024/EA04; 4B024/GA11; 4B024/HA08; 4B065/AA01X; 4B065/AA57X; 4B065/AA72X; 4B065/AA87X; 4B065/AB01; 4B065/BA02; 4B065/CA24; 4B065/CA44; 4B065/CA46; 4C076/AA95; 4C076/CC01; 4C076/CC07; 4C076/CC09; 4C076/CC11; 4C076/CC16; 4C076/CC18; 4C076/CC21; 4C076/CC27; 4C076/CC31; 4C076/EE59N; 4C084/AA02; 4C084/AA03; 4C084/AA13; 4C084/BA03; 4C084/CA62; 4C084/DC50; 4C084/MA05; 4C084/NA14; 4C084/ZA011; 4C084/ZA012; 4C084/ZA361; 4C084/ZA362; 4C084/ZA671; 4C084/ZA672; 4C084/ZA891; 4C084/ZA892; 4C084/ZA941; 4C084/ZA942; 4C084/ZB071; 4C084/ZB072; 4C084/ZB261; 4C084/ZB262; 4C084/ZB331; 4C084/ZB332; 4C084/ZB351; 4C084/ZB352; 4C084/ZC211; 4C084/ZC212; 4C086/AA01; 4C086/AA02; 4C086/EA16; 4C086/MA01; 4C086/MA04; 4C086/NA14; 4C086/ZA01; 4C086/ZA36; 4C086/ZA67; 4C086/ZA89; 4C086/ZA94; 4C086/ZB07; 4C086/ZB26; 4C086/ZB33; 4C086/ZB35; 4C086/ZC21; 4H045/AA10; 4H045/AA30; 4H045/BA41; 4H045/EA20; 4H045/EA50; 4H045/FA74	<--

AB The invention concerns a process for specifically modulating the properties of an **intracellular target mol.** T, and/or of a cellular component C which interacts directly or indirectly in a cell with T, said process comprising: introducing into a cell a chimeric **mol.**, a so-called **targeted** effector, comprising a **recognition moiety** R having the capacity to specifically interact, within the cell, with a site on an **intracellular target mol.** T, R interacting with T with a first affinity A1 and an effector **moiety**, E, **covalently linked** to said **recognition moiety** R, E being a **mol.**, or a portion thereof, which has an initial capacity to exert an effect on at least one **mol.** M, and which when it is **covalently linked** to R, acquires the capacity to specifically exert the effect on the

intracellular target mol. T,wherein the
targeted effector interacts with T with a second affinity A2, the
affinity A1 or the affinity A2 corresponding to a Kd of less than 1 x 10-8
M, and the properties of T and/or of C are specifically modulated by the
effector **moiety** E.
ST compd modulation affinity fusion **peptide** genetic method drug
screening
IT **Reaction kinetics**
(Kd; **targeted** modification of **intracellular**
compds.)
IT **Protein motifs**
(PTD(**protein** transduction **domain**); **targeted**
modification of **intracellular** compds.)
IT Gene, animal
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL
(Biological study)
(**cdk2**; **targeted** modification of
intracellular compds.)
IT **Bond**
(**covalent**; **targeted** modification of
intracellular compds.)
IT Immunity
Metabolism, animal
(disorder; **targeted** modification of **intracellular**
compds.)
IT Fusion **proteins** (chimeric **proteins**)
RL: BSU (Biological study, unclassified); PRP (Properties); THU
(Therapeutic use); BIOL (Biological study); USES (Uses)
(expression of; **targeted** modification of
intracellular compds.)
IT Infection
(fungal; **targeted** modification of **intracellular**
compds.)
IT Disease, animal
(genetic; **targeted** modification of **intracellular**
compds.)
IT Infection
(microbial; **targeted** modification of **intracellular**
compds.)
IT **Molecules**
(phosphorylated; **targeted** modification of
intracellular compds.)
IT **Conformation**
(**protein**; **targeted** modification of
intracellular compds.)
IT **Proteins**
RL: ARU (Analytical role, unclassified); PRP (Properties); ANST
(Analytical study)
(regulatory, transcription; **targeted** modification of
intracellular compds.)
IT Affinity
Animal cell
Bond cleavage
Cardiovascular system, disease
Cell membrane
DNA sequences
Dimerization
Drug screening
Eukaryota
Genetic methods
Genetic vectors
Gingiva, disease
Immunoassay

```
     Labels
     Muscle, disease
       **Mutagenesis**
     Neoplasm
     Nervous system, disease
     PCR (polymerase chain reaction)
     Phenotypes
     Prokaryote
       Protein motifs
     Recombination, genetic
     Secretion (process)
     Tooth, disease
        (targeted modification of intracellular compds.)
IT   Peptides, analysis
     RL: ANT (Analyte); BPN (Biosynthetic preparation); CPS (Chemical process);
     PEP (Physical, engineering or chemical process); PRP (Properties); ANST
     (Analytical study); BIOL (Biological study); PREP (Preparation); PROC
     (Process)
        (targeted modification of intracellular compds.)
IT   Carbohydrates, analysis
     Lipids, analysis
     Nucleic acids
       Proteins
     RL: ANT (Analyte); CPS (Chemical process); PEP (Physical,
     engineering or chemical process); PRP (Properties); ANST (Analytical
     study); PROC (Process)
        (targeted modification of intracellular compds.)
IT   Enzymes, analysis
     RL: ARU (Analytical role, unclassified); PRP (Properties); ANST
     (Analytical study)
        (targeted modification of intracellular compds.)
IT   Radionuclides, uses
     RL: NUU (Other use, unclassified); PRP (Properties); USES (Uses)
        (targeted modification of intracellular compds.)
IT   Amino acids, properties
       Thioredoxins
     RL: PRP (Properties)
        (targeted modification of intracellular compds.)
IT   Proteins
     RL: NUU (Other use, unclassified); PRP (Properties); USES (Uses)
        (tracer; targeted modification of intracellular
        compds.)
IT   Infection
        (viral; targeted modification of intracellular
        compds.)
IT   425433-99-4, 1: PN: EP1205191 PAGE: 15 unclaimed DNA   425434-00-0
     425434-01-1, 3: PN: EP1205191 PAGE: 15 unclaimed DNA   425434-02-2
     425434-03-3   425434-04-4   425434-05-5   425434-06-6
     RL: PRP (Properties)
        (unclaimed nucleotide sequence; targeted modification of
        intracellular compds.)
RE.CNT  4     THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
```


(1) Cohen, B; PROC NATL ACAD SCI U S A 1998, V95(24), P14272 HCAPLUS
(2) Colas, P; CURR OPIN CHEM BIOL 2000, V4(1), P54 HCAPLUS
(3) Colas, P; NATURE (LONDON) 1996, V380(6574), P548 HCAPLUS
(4) Colas, P; TRENDS BIOTECHNOL 1998, V16(8), P355 HCAPLUS

L79 ANSWER 5 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **2002:276898** HCAPLUS
DN **137:3514**
ED Entered STN: 14 Apr 2002
TI **Thioredoxin** superfamily and p53 against oxidative stresses

AU Ueno, Masaya; Nakamura, Hajime; Masutani, Hiroshi; Ueda, Shugo; Yodoi, Junji
CS Department of Gastroenterological Surgery, Kyoto University Graduate School of Medicine, Kyoto, 606-8397, Japan
SO Recent Research Developments in Immunology (2000), 2(Pt. 1), 375-381
CODEN: RRDIB8
PB Research Signpost
DT Journal; General Review
LA English
CC 13-0 (Mammalian Biochemistry)
Section cross-reference(s): 3
AB A review with 28 refs. The tumor suppressor gene product, p53, controls the cell cycle progression in G1 phase and suppresses cell proliferation through the expression of cell cycle-related genes. Various mechanisms have been proposed how p53 protects cells against many stimuli, including oxidative stress. The protein level and the promoter activity of p53 are enhanced in response to various stimuli, including DNA damaging agents or in the cellular reduction/oxidation (redox) status. Cellular redox status is regulated by thiols such as glutathione and **thioredoxin** (**TRX**). **TRX** has a redox-active disulfide/dithiol within its highly conserved active site sequence: -Cys-Gly-**Pro**-Cys-, and exerts protein-disulfide reduction together with NADPH and **TRX** reductase. **TRX** functions as a dithiol hydrogen donor for cellular proteins, such as ribonucleotide reductase, which is essential for DNA synthesis. **TRX** is induced by various oxidative stress. In addition, **TRX** translocates from the cytoplasm into the nucleus in response to oxidative stress. In the nucleus, **TRX** enhances the DNA binding activity of several transcriptional factors with or without Ref-1 (redox factor-1)/APEX located in the nucleus. It has been also clarified that Ref-1 or **TRX** regulates the DNA binding activity of p53. Recently there are growing members of **thioredoxin** superfamily which share similar active sites; -Cys-X1-X2-Cys- and similar three dimensional structures. Accumulated results suggest that **TRX** superfamily members play regulatory roles in the signal transduction of **apoptosis**/cell death or DNA repair by affecting the activity of p53.
ST review **thioredoxin** superfamily p53 oxidative stress apoptosis DNA repair
IT Enzyme functional sites
(active; **thioredoxin** superfamily share similar active sites)
IT Biological transport
(**intracellular**, translocation from cytoplasm into nucleus; **thioredoxins**, induced by oxidative stress, affect p53 activity thus regulating apoptosis and DNA repairs)
IT Apoptosis
DNA repair
Oxidative stress, biological
(**thioredoxins**, induced by oxidative stress, affect p53 activity thus regulating apoptosis and DNA repairs)
IT **Thioredoxins**
Transcription factors
p53 (protein)
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(**thioredoxins**, induced by oxidative stress, affect p53 activity thus regulating apoptosis and DNA repairs)
RE.CNT 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Akamatsu, Y; J Biol Chem 1997, V272, P14497 HCAPLUS
(2) Aslund, F; Proc Natl Acad Sci U S A 1994, V91, P9813 HCAPLUS
(3) Buttke, T; Immunol Today 1994, V15, P7 HCAPLUS
(4) Chae, H; Proc Natl Acad Sci USA 1994, V91, P7017 HCAPLUS
(5) Formigli, L; Microvasc Res 1998, V56, P277 MEDLINE

(6) Fuchs, S; Oncogene 1998, V17, P2543 HCAPLUS
(7) Hainaut, P; Cancer Res 1993, V53, P1739 HCAPLUS
(8) Hirota, K; Proc Natl Acad Sci USA 1997, V94, P3633 HCAPLUS
(9) Holmgren, A; Ann Rev Biochem 1985, V54, P237 MEDLINE
(10) Honda, R; Febs Lett 1997, V420, P25 HCAPLUS
(11) Jayaraman, L; Genes Dev 1997, V11, P558 HCAPLUS
(12) Laurent, T; J Biol Chem 1964, V239, P3436 HCAPLUS
(13) Lotem, J; Proc Natl Acad Sci U S A 1996, V93, P9166 HCAPLUS
(14) Makino, Y; J Clin Invest 1996, V98, P2469 HCAPLUS
(15) Matthews, J; Nucleic Acids Res 1992, V20, P3821 HCAPLUS
(16) Nakamura, H; Free Rad Biol Med, in press 1998, V24 HCAPLUS
(17) Nigam, S; J Biol Chem 1994, V269, P1744 HCAPLUS
(18) Pim, D; Oncogene 1997, V15, P257 HCAPLUS
(19) Rainwater, R; Mol Cell Biol 1995, V15, P3892 HCAPLUS
(20) Sachi, Y; Immunol Lett 1995, V44, P189 HCAPLUS
(21) Scheffner, M; Nature 1995, V373, P81 HCAPLUS
(22) Spyrou, G; J Biol Chem 1997, V272, P2936 HCAPLUS
(23) Tagaya, Y; EMBO J 1989, V8, P757 HCAPLUS
(24) Tanaka, T; Lab Invest 1997, V77, P145 HCAPLUS
(25) Taniguchi, Y; Nucleic Acid Res 1996, V24, P2746 HCAPLUS
(26) Tao, W; Proc Natl Acad Sci U S A 1999, V96, P6937 HCAPLUS
(27) Ueno, M; J Biol Chem 1999, V274, P35809 HCAPLUS
(28) Weinberg, W; Oncogene 1995, V10, P2271 HCAPLUS

L79 ANSWER 6 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:808579 HCAPLUS
DN 132:45818
ED Entered STN: 23 Dec 1999
TI Interaction trap systems for detecting protein interactions
IN **Brent, Roger**; McCoy, John M.; Jessen, Timm H.
PA General Hospital Corporation, USA; Genetics Institute, Inc.
SO U.S., 24 pp., Cont.-in-part of U.S. Ser. No. 278,082.
CODEN: USXXAM
DT Patent
LA English
IC ICM C12Q001-68
ICS C12Q001-00; C12N001-19; C12N005-16
NCL 435006000
CC 3-2 (Biochemical Genetics)
Section cross-reference(s): 6
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6004746	A	19991221	US 1995-504538	19950720
	EP 1405911	A1	20040407	EP 2003-21647	19950720
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE				
	ES 2210306	T3	20040701	ES 1995-928118	19950720
	US 6399296	B1	20020604	US 1996-630052	19960409
	US 6242183	B1	20010605	US 1999-249458	19990212
	US 2003113749	A1	20030619	US 2002-162538	20020604
PRAI	US 1994-278082	A2	19940720		
	EP 1995-928118	A3	19950720		
	US 1995-504538	A2	19950720		
	US 1996-630052	A1	19960409		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 6004746	ICM	C12Q001-68
	ICS	C12Q001-00; C12N001-19; C12N005-16
	NCL	435006000
US 6399296	ECLA	C12N009/02D; C12N015/10C6; C12Q001/68P
US 2003113749	ECLA	C12N009/02D; C12N015/10C6; C12Q001/02B; C12Q001/68P

AB The invention features a novel interaction trap system for the

identification and anal. of **conformationally**-constrained
proteins that either phys. interact with a second protein of interest or
that antagonize or agonize such an interaction. The system involves a
eukaryotic host strain (yeast) which is engineered to produce a protein of
therapeutic or diagnostic interest as a fusion product covalently bonded
to a known DNA binding domain. Said host strain also contains one or more
reporter genes whose transcription is detected in response to a bait-prey
interaction. Each candidate prey protein is **conformationally**
-constrained (for example, either by embedding the protein within a
conformation-constraining protein or by linking together the
protein's amino and carboxy termini) such that it is maintained in a
fixed, three-dimensional structure. Also disclosed are methods for
assaying protein interactions, and identifying antagonists and agonists of
protein interactions. Proteins isolated by these methods are also
discussed.

ST genetic engineering trap system protein interaction

IT **Proteins**, specific or class
RL: ARU (Analytical role, unclassified); BPN (Biosynthetic preparation); **BPR (Biological process)**; BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); **PROC (Process)**
(DNA-binding, chimeric bait proteins comprising DNA-binding moiety; interaction trap systems for detecting protein interactions)

IT Gene, microbial
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(RAS, in construction of bait vector in **thioredoxin** interaction trap; interaction trap systems for detecting protein interactions)

IT Ras proteins
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(bait in **thioredoxin** interaction trap; system for identification and anal. of **conformationally**-constrained proteins phys. interacting with second protein of interest or antagonizing or agonizing such interaction)

IT Fusion **proteins** (chimeric **proteins**)
RL: ARU (Analytical role, unclassified); BPN (Biosynthetic preparation); **BPR (Biological process)**; BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); **PROC (Process)**
(bait; interaction trap systems for detecting protein interactions)

IT **Thioredoxins**
RL: ARU (Analytical role, unclassified); BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process)
(**conformationally**-constrained protein; interaction trap systems for detecting protein interactions)

IT **Proteins**, general, biological studies
RL: **BPR (Biological process)**; BSU (Biological study, unclassified); BIOL (Biological study); **PROC (Process)**
(detecting protein interactions of; interaction trap systems for detecting protein interactions)

IT Chimeric gene
RL: ARU (Analytical role, unclassified); BPN (Biosynthetic preparation); ANST (Analytical study); BIOL (Biological study); PREP (Preparation)
(encoding chimeric bait protein; interaction trap systems for detecting protein interactions)

IT Saccharomyces
(host system; interaction trap systems for detecting protein interactions)

IT Genetic engineering
(interaction trap systems for detecting protein interactions)

IT Gene, microbial

RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(lexA, in construction of bait vector in **thioredoxin** interaction trap; interaction trap systems for detecting protein interactions)

IT Animal cell
(mammalian, host system; interaction trap systems for detecting protein interactions)

IT **Conformation**
(protein, constrained; system for identification and anal. of **conformationally**-constrained proteins phys. interacting with second protein of interest or antagonizing or agonizing such interaction)

IT **Proteins**, specific or class
RL: ARU (Analytical role, unclassified); BPN (Biosynthetic preparation); **BPR (Biological process)**; BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); **PROC (Process)**
(**thioredoxin** homolog, **conformationally**-constrained protein; interaction trap systems for detecting protein interactions)

IT Gene, microbial
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(trxA, in construction of prey vector in **thioredoxin** interaction trap; interaction trap systems for detecting protein interactions)

IT Reporter gene
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(use in signaling protein interaction; interaction trap systems for detecting protein interactions)

IT **175799-54-9 175799-55-0 175799-56-1**
175923-57-6 176086-89-8 176086-91-2
RL: ANT (Analyte); BPR (Biological process); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PROC (Process)
(amino acid sequence; interaction trap system for detecting protein interactions and sequences of exemplary **Cdk2**-interacting peptides)

IT **175799-51-6**
RL: ANT (Analyte); BPR (Biological process); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PROC (Process)
(amino acid sequence; interaction trap system for detecting protein interactions,and sequences of exemplary **Cdk2**-interacting peptides)

IT **175799-49-2**
RL: PRP (Properties)
(bait in **thioredoxin** interaction trap; interaction trap systems for detecting protein interactions)

IT **141349-86-2**
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(bait in **thioredoxin** interaction trap; system for identification and anal. of **conformationally**-constrained proteins phys. interacting with second protein of interest or antagonizing or agonizing such interaction)

IT 197868-77-2, GenBank I44530 252909-88-9, 1: PN: US6004746 SEQID: 4 unclaimed DNA 252909-89-0
RL: PRP (Properties)
(unclaimed nucleotide sequence; interaction trap systems for detecting protein interactions)

IT 117525-18-5 175923-55-4 175923-56-5 175923-58-7 175923-59-8 176086-88-7
RL: PRP (Properties)
(unclaimed protein sequence; interaction trap systems for detecting protein interactions)

IT 252852-68-9 252852-70-3 252852-71-4
RL: PRP (Properties)
(unclaimed sequence; interaction trap systems for detecting protein interactions)
RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Bartel; Cellular Interaction in Development: A Practical Approach 1993, P153 HCAPLUS
(2) Berger; Cell 1992, V70, P251 HCAPLUS
(3) Bishop, J; Science 1987, V235, P305 HCAPLUS
(4) Brent; US 4833080 1989 HCAPLUS
(5) Brent; Cell 1985, V43, P729 HCAPLUS
(6) Brent; Nature 1984, V312, P612 HCAPLUS
(7) Broach; Gene 1979, V8, P121 HCAPLUS
(8) Celenza; Cellular Biology 1989, V9, P5045 HCAPLUS
(9) Celenza; Science 1986, V233, P1175 HCAPLUS
(10) Chakraborty; J Biol Chem 1992, V267, P17498 HCAPLUS
(11) Draetta; Trends in Biochem Soc 1990, V15, P378 HCAPLUS
(12) Fearon; Proc Natl Acad Sci USA 1992, V89, P7958 HCAPLUS
(13) Fields; US 5283173 1994 HCAPLUS
(14) Fields; Nature 1989, V340, P245 HCAPLUS
(15) Fields; Trends In Genetics 1994, V10, P286 HCAPLUS
(16) Finkel; J Biol Chem 1993, V268(1), P5 HCAPLUS
(17) Gill; Nature 1988, V334, P721 HCAPLUS
(18) Giniger; Cell 1985, V40, P767 HCAPLUS
(19) Gyuris; Cell 1993, V75, P791 HCAPLUS
(20) Hadwiger; Proc Natl Acad Sci USA 1989, V86, P6255 HCAPLUS
(21) Hansen; Cell 1988, V53, P172 HCAPLUS
(22) Harper; Cell 1993, V75, P805 HCAPLUS
(23) Hartley; Cellular Interaction in Development A Practical Approach 1994, P153
(24) Housey; US 4980281 1990 HCAPLUS
(25) Koff; Cell 1991, V66, P1217 HCAPLUS
(26) La Vallie; Bio/Technology 1993, V11, P187 HCAPLUS
(27) Lech; Cell 1988, V52, P179 HCAPLUS
(28) Levine; Cell 1989, V59, P405 HCAPLUS
(29) McCoy; US 5270181 1993 HCAPLUS
(30) Meyerson; The EMBO Journal 1992, V11, P2909 HCAPLUS
(31) Pines; Cell 1989, V59, P833
(32) Reddy; Proc Natl Acad Sci USA 1983, V80, P2500 HCAPLUS
(33) Richardson; Cell 1989, V59, P1127 HCAPLUS
(34) Richardson; Genes & Development 1990, V4, P1332 HCAPLUS
(35) Struhl, K; Annu Rev Biochem 1989, V58, P1051 HCAPLUS
(36) Struhl, K; Nature 1988, V332, P649 HCAPLUS
(37) Touchette; The Journal of NIH Research 1991, V3, P44
(38) Tsai; Nature 1991, V353, P174 HCAPLUS
(39) Van Beveren; Cell 1983, V32, P1241 HCAPLUS
(40) Wittenberg; Cell 1988, V54, P1061 HCAPLUS
(41) Wittenberg; Cell 1990, V62, P225 HCAPLUS
(42) Wittenberg; Molecular and Cellular Biology 1989, V9, P4064 HCAPLUS
(43) Xiong; Cell 1991, V65, P691 HCAPLUS
(44) Yang; Science 1992, V257, P680 HCAPLUS
(45) Zervos; Cell 1993, V72, P223 HCAPLUS

L79 ANSWER 7 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:684519 HCAPLUS
DN 127:355925
ED Entered STN: 29 Oct 1997
TI Interaction trap systems for detecting protein interactions
IN **Brent, Roger**; McCoy, John M.; Jessen, Timm H.; Xu, Chanxing Wilson
PA General Hospital Corp., USA; Genetics Institute, Inc.
SO PCT Int. Appl., 89 pp.

```
     CODEN: PIXXD2
DT   Patent
LA   English
IC   ICM  C12Q001-00
     ICS  C12Q001-68; G01N033-53; C12P021-00; C12N001-19; C12N001-21;
          C12N005-10
CC   3-1 (Biochemical Genetics)
     Section cross-reference(s): 9
FAN.CNT 4
     PATENT NO.          KIND   DATE         APPLICATION NO.        DATE
     ---------------     ----   --------     --------------------   --------
PI   WO 9738127           A1    19971016     WO 1997-US5793         19970409
         W:  JP
         RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
     US 6399296           B1    20020604     US 1996-630052         19960409
     EP 904402            A1    19990331     EP 1997-917897         19970409
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI
     JP 2000508174        T2    20000704     JP 1997-536441         19970409
PRAI US 1996-630052       A     19960409
     US 1994-278082       A2    19940720
     US 1995-504538       A2    19950720
     WO 1997-US5793       W     19970409
CLASS
 PATENT NO.       CLASS  PATENT FAMILY CLASSIFICATION CODES
 --------------   -----  ----------------------------------------------
 WO 9738127       ICM    C12Q001-00
                  ICS    C12Q001-68; G01N033-53; C12P021-00; C12N001-19;
                         C12N001-21; C12N005-10
 WO 9738127       ECLA   C12N009/02D; C12Q001/02B; C12Q001/68P
 US 6399296       ECLA   C12N009/02D; C12N015/10C6; C12Q001/68P
```

AB A method is disclosed of determining whether a first protein is capable of phys. interacting with a second protein, involving: (a) providing a host cell which contains (i) a reporter gene operably linked to a protein binding site; (ii) a first fusion gene which expresses a first fusion protein, the first fusion protein including the first protein covalently bonded to a binding moiety which is capable of specifically binding to the protein binding site; and (iii) a second fusion gene which expresses a second fusion protein, the second fusion protein including the second protein covalently bonded to a gene activating moiety and being **conformationally**-constrained; and (b) measuring expression of the reporter gene as a measure of an interaction between the first and the second proteins. Also disclosed are methods for assaying protein interactions, and identifying antagonists and agonists of protein interactions. Proteins isolated by these methods are also discussed. Finally, populations of eukaryotic cells are disclosed, each cell having a recombinant DNA mol. encoding a **conformationally**-constrained **intracellular** peptide. Thus, a **thioredoxin** trap system is demonstrated using **Cdk2** and Ras baits, the DNA-binding protein domain of LexA, **thioredoxin** and the **conformation** -constraining protein, and LEU2 or lacZ as reporter genes in yeast host cells. Peptide aptamers binding to the **Cdk2** bait were detected from a peptide library and studied for functional inhibition of **Cdk2**.

ST protein interaction detection trap system; **Cdk2** interaction peptide aptamer trap system; Ras interaction peptide aptamer trap system; **thioredoxin** interaction trap system protein; peptide library protein interaction trap system

IT **Protein motifs**
(DNA-binding domains; interaction trap systems for detecting protein interactions)

IT Gene, microbial
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)

(LEU2, reporter; interaction trap systems for detecting protein interactions)

IT **Thioredoxins**
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(**conformation**-constraining fusion protein moiety; interaction trap systems for detecting protein interactions)

IT Affinity chromatography
DNA sequences
(encoding peptides interacting with **Cdk2** bait in interaction trap systems for detecting protein interactions)

IT Transcription factors
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(gene lexA, DNA-binding domain; interaction trap systems for detecting protein interactions)

IT Yeast
(host cell; interaction trap systems for detecting protein interactions)

IT Immunoassay
(immunoblotting; encoding peptides interacting with **Cdk2** bait in interaction trap systems for detecting protein interactions)

IT Immunoassay
(immunopptn.; encoding peptides interacting with **Cdk2** bait in interaction trap systems for detecting protein interactions)

IT Peptide library
(interaction trap systems for detecting protein interactions)

IT Reporter gene
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(interaction trap systems for detecting protein interactions)

IT **Proteins**, general, biological studies
Ras **proteins**
RL: **BPR (Biological process)**; BSU (Biological study, unclassified); BIOL (Biological study); **PROC (Process)**
(interaction trap systems for detecting protein interactions)

IT Gene, microbial
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(lacZ, reporter; interaction trap systems for detecting protein interactions)

IT Ras **proteins**
RL: **BPR (Biological process)**; BSU (Biological study, unclassified); BIOL (Biological study); **PROC (Process)**
(p21c-Ha-ras; interaction trap systems for detecting protein interactions)

IT Plasmid vectors
(pBRM116-H-Ras(G12V), containing Ras bait; encoding peptides interacting with **Cdk2** bait in interaction trap systems for detecting protein interactions)

IT Plasmid vectors
(pEG202-H-Ras(G12V), containing Ras bait; encoding peptides interacting with **Cdk2** bait in interaction trap systems for detecting protein interactions)

IT Plasmid vectors
(pJM-1, containing **Cdk2** bait; encoding peptides interacting with **Cdk2** bait in interaction trap systems for detecting protein interactions)

IT **Molecular association**
(protein-protein; interaction trap systems for detecting protein interactions)

IT **141349-86-2**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(interaction trap systems for detecting protein interactions)

IT **175799-49-2 175799-51-6 175799-52-7**
175799-53-8 175799-54-9 175799-55-0

175799-56-1 175799-57-2 175799-58-3
175799-59-4 175833-98-4 175923-56-5 175923-57-6
176086-88-7 176086-89-8 176086-91-2 198268-45-0
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(peptide aptamer binding to **Cdk2** bait; encoding peptides interacting with **Cdk2** bait in interaction trap systems for detecting protein interactions)

L79 ANSWER 8 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **1997:244532** HCAPLUS
DN **126:304647**
ED Entered STN: 16 Apr 1997
TI Redox regulation of cellular activation
AU Nakamura, Hajime; Nakamura, Kazuhiro; Yodoi, Junji
CS Inst. Virus Res., Kyoto Univ., Kyoto, 606-01, Japan
SO Annual Review of Immunology (1997), 15, 351-369
CODEN: ARIMDU; ISSN: 0732-0582
PB Annual Reviews
DT Journal; General Review
LA English
CC 15-0 (Immunochemistry)
Section cross-reference(s): 13
AB A review with 93 refs. Growing evidence has indicated that cellular reduction/oxidation(redox) status regulates various aspects of cellular function.
Oxidative stress can elicit pos. responses such as cellular proliferation or activation, as well as neg. responses such as growth inhibition or cell death. Cellular redox status is maintained by **intracellular** redox-regulating **mols.**, including **thioredoxin** (**TRX**). **TRX** is a small multifunctional protein that has a redox-active disulfide/dithiol within the conserved active site sequence: Cys-Gly-**Pro**-Cys. Adult T cell leukemia-derived factor (ADF), which we originally defined as an IL-2 receptor α-chain/Tac inducer produced by human T cell lymphotrophic virus-I (HTLV-I)-transformed T cells, has been identified as human **TRX. TRX**/ADF is a stress-inducible protein secreted from cells. **TRX**/ADF has both **intracellular** and extracellular functions as one of the key regulators of signaling in the cellular responses against various stresses. Extracellularly, **TRX**/ADF shows a cytoprotective activity against oxidative stress-induced **apoptosis** and a growth-promoting effect as an autocrine growth factor. **Intracellularly**, **TRX**/ADF is involved in the regulation of protein-protein or protein-nucleic acid interactions through the reduction/oxidation of protein cysteine residues. For example, **TRX**/ADF translocates from the cytosol into the nucleus by a variety of cellular stresses, to regulate the expression of various genes through the redox factor-1 (Ref-1)/APEX. Further studies to clarify the regulatory roles of **TRX**/ADF and its **target mols.** may elucidate the **intracellular** signaling pathways in the responses against various stresses. The concept of "redox regulation" is emerging as an understanding of the novel mechanisms in the pathogenesis of several disorders, including viral infections, immunodeficiency, malignant transformation, and degenerative disease.
ST review redox regulation cell activation **thioredoxin**
IT Cytokines
Cytokines
Thioredoxins
Thioredoxins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**ADF (adult T cell leukemia-derived factor)**; redox regulation

of cellular activation in relation to **thioredoxin** and adult
T-cell leukemia-derived factor)

IT Cell activation
(redox regulation of cellular activation in relation to
thioredoxin and adult T-cell leukemia-derived factor)

IT **Thioredoxins**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(redox regulation of cellular activation in relation to
thioredoxin and adult T-cell leukemia-derived factor)

L79 ANSWER 9 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **1997:109932** HCAPLUS
DN **126:195852**
ED Entered STN: 15 Feb 1997
TI Targeting vectors for intracellular immunization
AU Persic, Lidija; Righi, Massimo; Roberts, Andy; Hoogenboom, Hennie R.; Cattaneo, Antonino; Bradbury, Andrew
CS Societa Italiana per la Ricerca Scientifica, Via G. Paisiello 47C, Rome, 00198, Italy
SO Gene (1997), 187(1), 1-8
CODEN: GENED6; ISSN: 0378-1119
PB Elsevier
DT Journal
LA English
CC 3-2 (Biochemical Genetics)
Section cross-reference(s): 15

AB **Intracellular** immunization is defined as the inhibition or inactivation of the function of a **mol.** by the ectopic **intracellular** expression of antibody binding **domains** which **recognize** the **mol.** Such recombinant antibodies can be directed to different compartments of eukaryotic cells by previously defined **targeting** signals, thus permitting the study of any **mol.** in any cellular compartment for which an antibody is available. For this purpose, a set of vectors was created based on the VHExpress vector described by L. Persic et al. (1997), which has been modified to express scFvs (single chain fragments) **linked** to specific **targeting** signals. These permit the localization of scFvs to different **intracellular** compartments: the endoplasmic reticulum (scFvE-er), the nucleus (scFvE-nuclear), the mitochondria (scFvE-mit), the cytoplasm (scFvE-cyto), and as secreted **proteins** (scFvE-sec). The function of these vectors was assessed by the immunofluorescence of COS cells transiently transfected with constructs containing the αD11 scFv.

ST intracellular immunization antibody targeting vector cloning; endoplasmic reticulum targeting vector antibody cloning; nucleus targeting vector antibody cloning; mitochondria targeting vector antibody cloning; cytoplasm targeting vector antibody cloning; secretion targeting vector antibody cloning

IT **Protein motifs**
(endoplasmic reticulum retention signal; subcellular targeting vectors for intracellular immunization with single-chain Fv antibodies)

IT Immunization
(intracellular; subcellular targeting vectors for intracellular immunization with single-chain Fv antibodies)

IT **Protein motifs**
(mitochondrial signal; subcellular targeting vectors for intracellular immunization with single-chain Fv antibodies)

IT **Protein motifs**
(nuclear localization sequence; subcellular targeting vectors for intracellular immunization with single-chain Fv antibodies)

IT Secretion (process)
(**protein**; subcellular targeting vectors for intracellular

immunization with single-chain Fv antibodies)
IT Plasmid vectors
(scFvExpress-cyto; subcellular targeting vectors for intracellular immunization with single-chain Fv antibodies)
IT Plasmid vectors
(scFvExpress-er; subcellular targeting vectors for intracellular immunization with single-chain Fv antibodies)
IT Plasmid vectors
(scFvExpress-mit; subcellular targeting vectors for intracellular immunization with single-chain Fv antibodies)
IT Plasmid vectors
(scFvExpress-nuc; subcellular targeting vectors for intracellular immunization with single-chain Fv antibodies)
IT Plasmid vectors
(scFvExpress-sec; subcellular targeting vectors for intracellular immunization with single-chain Fv antibodies)
IT Antibodies
RL: BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(single chain; subcellular targeting vectors for intracellular immunization with single-chain Fv antibodies)
IT Cell nucleus
Cytoplasm
Endoplasmic reticulum
Mitochondria
Molecular cloning
(subcellular **targeting** vectors for **intracellular** immunization with single-chain Fv antibodies)
IT Leader **peptides**
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(subcellular targeting vectors for intracellular immunization with single-chain Fv antibodies)

L79 ANSWER 10 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:262865 HCAPLUS
DN 124:309558
ED Entered STN: 04 May 1996
TI Interaction trap systems for detecting protein interactions
IN **Brent, Roger**; McCoy, John M.; Jessen, Timm H.; Xu, Chanxing Wilson
PA General Hospital Corporation, USA; Genetics Institute, Inc.
SO PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07H021-04
ICS C07K019-00; C12N001-19; C12N005-10; C12Q001-68; G01N033-68
CC 3-1 (Biochemical Genetics)
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9602561	A1	19960201	WO 1995-US9307	19950720
	W: JP				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	EP 773952	A1	19970521	EP 1995-928118	19950720
	EP 773952	B1	20031112		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	JP 10504713	T2	19980512	JP 1995-505277	19950720
	AT 254136	E	20031115	AT 1995-928118	19950720
	EP 1405911	A1	20040407	EP 2003-21647	19950720
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE				

```
     ES 2210306            T3     20040701    ES 1995-928118         19950720
     HK 1012006            A1     20040702    HK 1998-113236         19981211
     US 6242183            B1     20010605    US 1999-249458         19990212
PRAI US 1994-278082        A      19940720
     EP 1995-928118        A3     19950720
     WO 1995-US9307        W      19950720
CLASS
 PATENT NO.       CLASS  PATENT FAMILY CLASSIFICATION CODES
 --------------   -----  ---------------------------------------------
 WO 9602561       ICM    C07H021-04
                  ICS    C07K019-00; C12N001-19; C12N005-10; C12Q001-68;
                         G01N033-68
```

AB A method of determining protein interactions is described. This system includes
a host cell containing a reporter gene operably linked to a protein binding site, a first fusion gene which expresses a first protein covalently bonded to a binding moiety which is capable of specifically binding to the protein binding site, and a second fusion gene which expresses a second fusion protein covalently bonded to a gene activating moiety and is **conformationally**-constrained [protein has reduced structural flexibility involving disulfide bonds]. Expression of the reporter gene is measured by color reactions and cell viability assays. In addition to measuring protein interactions, antagonists and agonists of protein interactions may also be identified. Proteins sequences isolated by these methods are also presented. In addition the authors discuss the use of "bait" and "prey" domains.

ST protein interaction detection method interaction trap; **conformational** constraint protein interaction method **Thioredoxin**; **cdk2** phosphoprotein p12RAS interaction method detection; disulfide bond **conformation** constraint method **thioredoxin**

IT Genetic element
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(DNA-binding-protein recognition site; **Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and prey domains)

IT Protein sequences
(**Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and prey domains)

IT Proteins, specific or class
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(**Thioredoxin**-like proteins; **Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and prey domains)

IT Ribonucleic acid formation factors
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation); PROC (Process)
(activator; **Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and prey domains)

IT **Thioredoxins**
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); BIOL (Biological study); PREP (Preparation); USES (Uses)
(as **conformationally**-constrained peptide; **Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and

prey domains)

IT Saccharomyces cerevisiae
(as host cell; **Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and prey domains)

IT **Molecular association**
(between first fusion protein and second fusion protein; **Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and prey domains)

IT **Proteins**, specific or class
RL: BAC (Biological activity or effector, except adverse); **BPR (Biological process)**; BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation); **PROC (Process)**
(**conformationally**-constrained protein; **Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and prey domains)

IT **Conformation and Conformers**
(constraint; **Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and prey domains)

IT Cell
Color
(reporter gene expression measurement by color reaction and cell viability; **Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and prey domains)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(reporter; **Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and prey domains)

IT Gene, microbial
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(LEU2, use as reporter gene; **Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and prey domains)

IT **Bond**
(**covalent**, of **intracellular** peptide to **conformationally**-constrained protein; **Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and prey domains)

IT Gene
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(expression, measured by color reaction and cell viability; **Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and prey domains)

IT **Proteins**, specific or class
RL: BOC (Biological occurrence); BPN (Biosynthetic preparation); **BPR (Biological process)**; BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); **PROC (Process)**
(fusion products, **Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and prey domains)

IT Phosphoproteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene **cdk2**, identification of proteins interacting with; **Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and prey domains)

IT Ribonucleic acid formation factors
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(gene lexA, DNA binding domain of; **Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and prey domains)

IT Gene, microbial
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(lacZ, use as reporter gene; **Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and prey domains)

IT G proteins (guanine nucleotide-binding proteins)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p21ras, identification of proteins interacting with; **Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and prey domains)

IT Nucleotides, biological studies
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(poly-, candidate interactor as proteins or polynucleotides or small mols.; **Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and prey domains)

IT Ribonucleic acid formation factors
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation); PROC (Process)
(repressors, **Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and prey domains)

IT **Bond**
(sulfur-sulfur, **intracellular** peptide is **conformationally**-constrained by disulfide bonds between cysteine residues; **Thioredoxin** interaction trap system for detecting protein interactions)

IT **175799-49-2**
RL: PRP (Properties)
(amino acid sequence of **conformationally**-constrained protein (seq1); **Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and prey domains)

IT 176086-91-2
RL: PRP (Properties)
(amino acid sequence of **conformationally**-constrained protein (seq10); **Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and prey domains)

IT **175799-54-9**
RL: PRP (Properties)
(amino acid sequence of **conformationally**-constrained protein (seq11); **Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and prey domains)

IT **175799-55-0**
RL: PRP (Properties)
(amino acid sequence of **conformationally**-constrained protein (seq12); **Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and prey domains)

IT **175799-56-1**
RL: PRP (Properties)
(amino acid sequence of **conformationally**-constrained protein (seq13); **Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and prey domains)

IT 176086-88-7
RL: PRP (Properties)
(amino acid sequence of **conformationally**-constrained protein (seq17) interacting with RAS; **Thioredoxin** interaction trap system for detecting protein interactions)

IT 175923-57-6
RL: PRP (Properties)
(amino acid sequence of **conformationally**-constrained protein (seq19); **Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and prey domains)

IT 175923-55-4
RL: PRP (Properties)
(amino acid sequence of **conformationally**-constrained protein (seq2); **Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and prey domains)

IT 176086-89-8
RL: PRP (Properties)
(amino acid sequence of **conformationally**-constrained protein (seq20); **Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and prey domains)

IT 175923-56-5
RL: PRP (Properties)
(amino acid sequence of **conformationally**-constrained protein (seq3); **Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and prey domains)

IT 175923-58-7
RL: PRP (Properties)
(amino acid sequence of **conformationally**-constrained protein (seq6) interacting with **Cdk2**; **Thioredoxin** interaction trap system for detecting protein interactions)

IT 175923-59-8
RL: PRP (Properties)
(amino acid sequence of **conformationally**-constrained protein (seq7) interacting with **Cdk2**; **Thioredoxin** interaction trap system for detecting protein interactions)

IT 175923-60-1
RL: PRP (Properties)
(amino acid sequence of **conformationally**-constrained protein (seq8) interacting with **Cdk2**; **Thioredoxin** interaction trap system for detecting protein interactions)

IT **175799-51-6**
RL: PRP (Properties)
(amino acid sequence of **conformationally**-constrained protein (seq9); **Thioredoxin** interaction trap system for detecting protein interactions by reporter gene colorimetric reaction or cell viability anal. and use of bait and prey domains)

L79 ANSWER 11 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:227625 HCAPLUS
DN 124:282875
ED Entered STN: 18 Apr 1996
TI Genetic selection of peptide aptamers that **recognize** and inhibit **cyclin-dependent kinase 2**
AU **Colas, Pierre**; **Cohen, Barak**; Jessen, Timm; Grishina, Irina; McCoy, John; **Brent, Roger**
CS Dep. Mol. Biol., Massachusetts General Hosp., Boston, MA, 02114, USA
SO Nature (London) (1996), 380(6574), 548-50
CODEN: NATUAS; ISSN: 0028-0836
PB Macmillan Magazines
DT Journal
LA English
CC 7-3 (Enzymes)
Section cross-reference(s): 3
AB A network of interacting proteins controls the activity of **cyclin-dependent kinase 2** (**Cdk2**) (refs 1, 2) and governs the entry of higher eukaryotic cells into S phase. Anal. of this and other genetic regulatory networks would be facilitated by **intracellular** reagents that **recognize** specific **targets** and inhibit specific network connections. We report here the expression of a combinatorial library of constrained 20-residue peptides displayed by the active-site loop of Escherichia coli **thioredoxin** and the use of a two-hybrid system to select those that bind human **Cdk2**. These peptide aptamers were designed to mimic the **recognition** function of the complementarity-determining regions of Igs. The aptamers **recognized** different epitopes on the **Cdk2** surface with equilibrium dissociation constant in the nanomolar range; those tested inhibited **Cdk2** activity. Our results show that peptide aptamers bear some analogies with monoclonal antibodies, with the advantages that they are isolated together with their coding genes, that their small size should allow their structures to be solved, and that they are designated to function inside cells.
ST human **cyclin dependent kinase** peptide inhibitors; **Cdk2** ligand peptide combinatorial library chem
IT Combinatorial library
(genetic selection of combinatorial library-derived peptide aptamers that **recognize** and inhibit human **cyclin-dependent kinase 2**)
IT Peptides, biological studies
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(genetic selection of combinatorial library-derived peptide aptamers that **recognize** and inhibit human **cyclin-dependent kinase 2**)
IT **175799-49-2P 175799-50-5P 175799-51-6P 175799-52-7P 175799-53-8P 175799-54-9P 175799-55-0P 175799-56-1P 175799-57-2P 175799-58-3P 175799-59-4P 175833-98-4P 175834-03-4P 175834-04-5P**
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(amino acid sequence of; genetic selection of combinatorial library-derived peptide aptamers that **recognize** and inhibit human **cyclin-dependent kinase 2**
)
IT **141349-86-2, Cyclin-dependent kinase**

2
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(genetic selection of combinatorial library-derived peptide aptamers that **recognize** and inhibit human **cyclin-dependent kinase 2**)

L79 ANSWER 12 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **1992:528604** HCAPLUS
DN **117:128604**
ED Entered STN: 04 Oct 1992
TI Domains responsible for the differential targeting of glucose transporter isoforms
AU Asano, Tomoichiro; Takata, Kuniaki; Katagiri, Hideki; Tsukuda, Katsunori; Lin, Jiann Liang; Ishihara, Hisamitsu; Inukai, Kouichi; Hirano, Hiroshi; Yazaki, Yoshio; Oka, Yoshitomo
CS Fac. Med., Univ. Tokyo, Tokyo, 113, Japan
SO Journal of Biological Chemistry (1992), 267(27), 19636-41
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
CC 13-2 (Mammalian Biochemistry)
AB Facilitative glucose transporter isoforms, GLUT1 and GLUT4, have different **intracellular** distributions despite their very similar structure. In insulin-responsive tissues such as adipose tissues and muscle, GLUT4 **protein** residues mainly in the **intracellular** region in a basal condition and is translocated to the plasma membrane upon stimulation of insulin. In contrast, GLUT1 **protein** was distributed about equally between plasma membranes and low d. microsomal membranes in 3T3-L1 adipocytes. Furthermore, GLUT1 and GLUT4 were reported to be differentially **targeted** to the plasma membrane and **intracellular** region, resp., when expressed in chinese hamster ovary cells and HepG2 cells. To elucidate the differential **intracellular targeting** mechanisms, several chimeric glucose transporters in which portions of GLUT4 are replaced with corresponding portions of GLUT1 have been stably expressed in Chinese hamster ovary cells. Immunofluorescence and immunoelectron microscopy as well as measurement of glucose transport activity revealed that two **domains** of GLUT4, which are not the NH2- or COOH-terminal **domain**, determine its **targeting** to the **intracellular** vesicles. The first **domain** contains the consensus of the leucine zipper structure, suggesting that a **dimer**-forming structure of the glucose transporter might be required for its proper **targeting.** The other **domain** contains 28 amino acids, nine of which are different between GLUT1 and GLUT4. Immunoelectron microscopy revealed that the chimeric transporters containing both of these two **domains** of GLUT1, only the first **domain** of GLUT1, and none of the **domains**, exhibited a different cellular distribution with approx. 65, 30, and 15% of the transporters apparently on the plasma membrane, resp. The addition of insulin did not alter the apparent cellular distributions of these chimeric transporters. These **domains** would be specifically **recognized** by **intracellular targeting** mechanisms in Chinese hamster ovary cells.
ST glucose transporter GLUT1 GLUT4 targeting domain; translocation glucose transporter GLUT1 GLUT4 sorting
IT Cell membrane
Microsome
(GLUT-1 and GLUT-4 glucose transporter isoforms differential targeting to, identification of **protein** domains responsible for)
IT **Glycoproteins**, specific or class
RL: BIOL (Biological study)
(GLUT-1 (glucose-transporting, 1), **intracellular**

```
        targeting of, protein domain responsible
        for, GLUT-4 protein in relation to)
IT   Glycophosphoproteins
     RL: BIOL (Biological study)
        (GLUT-4 (glucose-transporting, 4), intracellular
        targeting of, protein domain responsible
        for, GLUT-1 protein in relation to)
IT   Conformation and Conformers
        (leucine zipper, of GLUT-4 protein
        domain, intracellular targeting in relation
        to)
IT   Biological transport
        (translocation, of GLUT-1 and GLUT-4 glucose transporter isoforms,
        differential targeting in, identification of protein domains
        responsible for)


=> => d all tot

L88  ANSWER 1 OF 3  HCAPLUS  COPYRIGHT 2004 ACS on STN
AN   2000:138347  HCAPLUS
DN   132:262197
ED   Entered STN:  01 Mar 2000
TI   Combinatorial protein reagents to manipulate protein function
AU   Colas, Pierre
CS   Laboratoire de Biologie Moleculaire et Cellulaire, Ecole Normale
     Superieure, Lyon, 69364, Fr.
SO   Current Opinion in Chemical Biology (2000), 4(
     1), 54-59
     CODEN: COCBF4; ISSN: 1367-5931
PB   Elsevier Science Ltd.
DT   Journal; General Review
LA   English
CC   9-0 (Biochemical Methods)
AB   A review with 45 refs.  The design and use of combinatorial protein
     libraries has become a fast moving field in mol. biol.  Different exptl.
     systems supporting various selection schemes are now available.  The
     latest breakthroughs include evolutionary expts. to improve existing
     binding surfaces, selections of homodimerizing peptides, the use of
     peptide aptamers to disrupt protein interactions inside living cells, and
     functional selections of aptamers to probe regulatory networks.
ST   combinatorial protein library selection review
IT   Peptide library
        (selection of proteins from combinatorial protein libraries for binding
        to protein targets)
IT   Peptides, properties
     Proteins, general, properties
     RL: PRP (Properties)
        (selection of proteins from combinatorial protein libraries for binding
        to protein targets)
RE.CNT  45     THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Abedi, M; Nucleic Acids Res 1998, V26, P623 HCAPLUS
(2) Aramburu, J; Science 1999, V285, P2129 HCAPLUS
(3) Boder, E; Nat Biotechnol 1997, V15, P553 HCAPLUS
(4) Bottger, A; Curr Biol 1997, V7, P860 HCAPLUS
(5) Bottger, V; Oncogene 1996, V13, P2141 HCAPLUS
(6) Caponigro, G; Proc Natl Acad Sci USA 1998, V95, P7508 HCAPLUS
(7) Cohen, B; Proc Natl Acad Sci USA 1998, V95, P14272 HCAPLUS
(8) Colas, P; Nature 1996, V380, P548 HCAPLUS
(9) Colas, P; Trends Biotechnol 1998, V16, P355 HCAPLUS
(10) DeRisi, J; Science 1997, V278, P680 HCAPLUS
(11) Fabbrizio, E; Oncogene 1999, V18, P4357 HCAPLUS
```

(12) Fanning, A; J Clin Invest 1999, V103, P767 HCAPLUS
(13) Fasano, A; Trends Biotechnol 1998, V16, P152 HCAPLUS
(14) Finley, R; Proc Natl Acad Sci USA 1994, V91, P12980 HCAPLUS
(15) Geyer, C; Proc Natl Acad Sci USA 1999, V96, P8567 HCAPLUS
(16) Griffiths, A; Curr Opin Biotechnol 1998, V9, P102 HCAPLUS
(17) Gustin, M; Microbiol Mol Biol Rev 1998, V62, P1264 HCAPLUS
(18) Hanes, J; Proc Natl Acad Sci USA 1997, V94, P4937 HCAPLUS
(19) Hanes, J; Proc Natl Acad Sci USA 1998, V95, P14130 HCAPLUS
(20) Jermutus, L; Curr Opin Biotechnol 1998, V9, P534 HCAPLUS
(21) Kolonin, M; Proc Natl Acad Sci USA 1998, V95, P14266 HCAPLUS
(22) Kuo, C; Annu Rev Immunol 1999, V17, P149 HCAPLUS
(23) Lu, Z; Biotechnology 1995, V13, P366 HCAPLUS
(24) Lubkowski, J; Nat Struct Biol 1998, V5, P140 HCAPLUS
(25) Nemoto, N; FEBS Lett 1997, V414, P405 HCAPLUS
(26) Norman, T; Science 1999, V285, P591 HCAPLUS
(27) Norris, J; Science 1999, V285, P744 HCAPLUS
(28) Palu, G; J Biotechnol 1999, V68, P1 HCAPLUS
(29) Pelletier, J; Nat Biotechnol 1999, V17, P683 HCAPLUS
(30) Remy, I; Proc Natl Acad Sci USA 1999, V96, P5394 HCAPLUS
(31) Ripka, A; Curr Opin Chem Biol 1998, V2, P441 HCAPLUS
(32) Roberts, R; Curr Opin Chem Biol 1999, V3, P268 HCAPLUS
(33) Roberts, R; Proc Natl Acad Sci USA 1997, V94, P12297 HCAPLUS
(34) Rodi, D; Curr Opin Biotechnol 1999, V10, P87 HCAPLUS
(35) Rondot, S; J Mol Biol 1998, V279, P589 HCAPLUS
(36) Schier, R; J Mol Biol 1996, V263, P551 HCAPLUS
(37) Schneider, S; Nat Biotechnol 1999, V17, P170 HCAPLUS
(38) Stahl, S; Trends Biotechnol 1997, V15, P185 HCAPLUS
(39) Tomlinson, I; J Mol Biol 1996, V256, P813 HCAPLUS
(40) Vidal, M; Nucleic Acids Res 1999, V27, P919 HCAPLUS
(41) Wang, B; Proc Natl Acad Sci USA 1999, V96, P9568 HCAPLUS
(42) Xie, M; Nat Biotechnol 1997, V15, P768 HCAPLUS
(43) Xu, C; Proc Natl Acad Sci USA 1997, V94, P12473 HCAPLUS
(44) Yang, M; Nucleic Acids Res 1995, V23, P1152 HCAPLUS
(45) Zhang, Z; Curr Biol 1999, V9, P417 HCAPLUS

L88 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:765600 HCAPLUS
DN 130:121046
ED Entered STN: 08 Dec 1998
TI An artificial cell-cycle inhibitor isolated from a combinatorial library
AU **Cohen, Barak A.; Colas, Pierre; Brent, Roger**
CS Department of Molecular Biology, Massachusetts General Hospital, Boston, MA, 02114, USA
SO Proceedings of the National Academy of Sciences of the United States of America (**1998**), **95**(**24**), **14272** -14277
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
CC 6-3 (General Biochemistry)
AB Understanding the genetic networks that operate inside cells will require the dissection of interactions among network members. Here the authors describe a peptide aptamer isolated from a combinatorial library that distinguishes among such interactions. This aptamer binds to **cyclin-dependent kinase 2** (**Cdk2**) and inhibits its kinase activity. In contrast to naturally occurring inhibitors, such as p21Cip1, which inhibit the activity of **Cdk2** on all its substrates, inhibition by pep8 has distinct substrate specificity. The authors show that the aptamer binds to **Cdk2** at or near its active site and that its mode of inhibition is competitive. Expression of pep8 in human cells retards their progression through the G1 phase of the cell cycle. These results suggest that the

aptamer inhibits cell-cycle progression by blocking the activity of **Cdk2** on substrates needed for the G1-to-S transition. This work demonstrates the feasibility of selection of artificial proteins to perform functions not developed during evolution. The ability to select proteins that block interactions between a gene product and some partners but not others should make sophisticated genetic manipulations possible in human cells and other currently intractable systems.

ST aptamer pep8 cell cycle inhibitor **CDK2** kinase active site

IT Interphase (cell cycle)
(G1-phase, pep8 aptamer inhibiting G1 to S transition; artificial cell-cycle inhibitor isolated from combinatorial library)

IT Histones
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(H1, pep8 blocks **CDK2** kinase activity on histone H1; artificial cell-cycle inhibitor isolated from combinatorial library)

IT Interphase (cell cycle)
(S-phase, pep8 aptamer inhibiting G1 to S transition; artificial cell-cycle inhibitor isolated from combinatorial library)

IT Enzyme functional sites
(active, pep8 aptamer binding at; artificial cell-cycle inhibitor isolated from combinatorial library)

IT Peptides, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(aptamer; artificial cell-cycle inhibitor isolated from combinatorial library)

IT Cell cycle
Combinatorial library
(artificial cell-cycle inhibitor isolated from combinatorial library)

IT Cell proliferation
(pep8 aptamer inhibiting; artificial cell-cycle inhibitor isolated from combinatorial library)

IT **141349-86-2, Cyclin-dependent kinase 2**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(inhibiting actions of; artificial cell-cycle inhibitor isolated from combinatorial library)

RE.CNT 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Barry, M; Nat Med 1996, V2, P299 HCAPLUS
(2) Brandon, E; Curr Biol 1995, V5, P625 HCAPLUS
(3) Brandon, E; Curr Biol 1995, V5, P758 HCAPLUS
(4) Brent, R; Nature (London) 1984, V312, P612 HCAPLUS
(5) Burritt, J; Anal Biochem 1996, V238, P1 HCAPLUS
(6) Cheng, X; Proc Natl Acad Sci USA 1997, V94, P14120 HCAPLUS
(7) Colas, P; Nature (London) 1996, V380, P548 HCAPLUS
(8) Cortese, R; Curr Opin Biotechnol 1996, V7, P616 HCAPLUS
(9) DeBondt, H; Nature (London) 1993, V363, P595 HCAPLUS
(10) Dowdy, S; Cell 1993, V73, P499 HCAPLUS
(11) Dulic, V; Science 1992, V257, P1958 HCAPLUS
(12) Dynlacht, B; Genes Dev 1994, V8, P1772 HCAPLUS
(13) Ewen, M; Cell 1993, V73, P487 HCAPLUS
(14) Finley, R; Proc Natl Acad Sci USA 1994, V91, P12980 HCAPLUS
(15) Gyuris, J; Cell 1993, V75, P791 HCAPLUS
(16) Harper, J; Cell 1993, V75, P805 HCAPLUS
(17) Harper, J; Mol Biol Cell 1995, V6, P387 MEDLINE
(18) Heiskanen, T; J Virol 1997, V71, P3879 HCAPLUS
(19) Jeffery, P; Nature (London) 1995, V376, P313
(20) Koff, A; Science 1992, V257, P1689 HCAPLUS
(21) Koivunen, E; J Biol Chem 1993, V268, P20205 HCAPLUS
(22) Koivunen, E; J Cell Biol 1993, V124, P373

(23) Kolonin, M; Proc Natl Acad Sci USA 1998, V95, P14266 HCAPLUS
(24) Leanna, C; Nucleic Acids Res 1996, V24, P3341 HCAPLUS
(25) Leng, X; Curr Biol 1997, V7, P709 HCAPLUS
(26) Lorimer, I; Proc Natl Acad Sci USA 1996, V93, P14815 HCAPLUS
(27) Lukas, J; Genes Dev 1997, V11, P1479 HCAPLUS
(28) Lukas, J; Mol Cell Biol 1995, V15, P2600 MEDLINE
(29) Lundin, K; Immunology 1996, V89, P579 HCAPLUS
(30) McConnell, S; Gene 1994, V151, P115 HCAPLUS
(31) McConnell, S; J Mol Biol 1995, V250, P460 HCAPLUS
(32) McGregor, D; Mol Biotechnol 1996, V6, P155 HCAPLUS
(33) McLafferty, M; Gene 1993, V128, P29 HCAPLUS
(34) Miklos, G; Cell 1996, V86, P521 HCAPLUS
(35) Molkentin, J; Curr Opin Genet Dev 1996, V6, P445 HCAPLUS
(36) Morgan, D; Nature (London) 1995, V374, P131 HCAPLUS
(37) Ohtsubo, M; Mol Cell Biol 1995, V15, P2612 MEDLINE
(38) O'Neil, K; Proteins 1992, V14, P509 HCAPLUS
(39) Peletskaya, E; J Mol Biol 1997, V270, P374 HCAPLUS
(40) Polyak, K; Genes Dev 1994, V8, P9 HCAPLUS
(41) Sayle, R; Trends Biochem Sci 1995, V20, P333
(42) Struhl, K; Cell 1996, V84, P179 HCAPLUS
(43) Studier, F; J Mol Biol 1986, V189, P113 HCAPLUS
(44) Terskikh, A; Proc Natl Acad Sci USA 1997, V94, P1663 HCAPLUS
(45) van den Heuvel, S; Science 1993, V262, P2050 HCAPLUS
(46) Vidal, M; Proc Natl Acad Sci USA 1996, V93, P10315 HCAPLUS
(47) Weinberg, R; Cell 1995, V81, P323 HCAPLUS
(48) Welpy, J; Proteins 1996, V26, P262
(49) Wrighton, N; Science 1996, V273, P458 HCAPLUS
(50) Xu, C; Proc Natl Acad Sci USA 1997, V94, P12473 HCAPLUS

L88 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:518960 HCAPLUS
DN 129:160646
ED Entered STN: 20 Aug 1998
TI The impact of two-hybrid and related methods on biotechnology
AU **Colas, Pierre; Brent, Roger**
CS the Laboratoire de Biologie Moleculaire et Cellulaire, Lyon, 69364, Fr.
SO Trends in Biotechnology (**1998**), **16**(**8**),
355-363
CODEN: TRBIDM; ISSN: 0167-7799
PB Elsevier Science Ltd.
DT Journal; General Review
LA English
CC 16-0 (Fermentation and Bioindustrial Chemistry)
AB A review with 59 refs. Two-hybrid technol. has contributed significantly to the unraveling of mol. regulatory networks by facilitating the discovery of protein interactions. Outgrowths of these methods are developing rapidly, including interaction mating to identify false positives and map protein networks, two-bait systems, systems not based on transcription, and systems permitting the selection of peptide aptamers to manipulate gene and allele function. These advances promise to have a significant impact on industrial biotechnol. and drug development.
ST review biotechnol hybrid method
IT Biotechnology
Genetic selection
(impact of two-hybrid and related methods on biotechnol.)
RE.CNT 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE

(1) Allen, J; Trends Biochem Sci 1995, V20, P511 HCAPLUS
(2) Aronheim, A; Mol Cell Biol 1997, V17, P3094 HCAPLUS
(3) Balzi, E; J Bioenerg Biomembr 1995, V27, P71 HCAPLUS
(4) Bartel, P; BioTechniques 1993, V14, P920 MEDLINE
(5) Bartel, P; Nat Genet 1996, V12, P72 HCAPLUS
(6) Boeke, J; Mol Gen Genet 1984, V197, P345 HCAPLUS

(7) Boguslawski, G; Mol Gen Genet 1985, V199, P401 HCAPLUS
(8) Brendel, M; Mol Gen Genet 1976, V147, P209 HCAPLUS
(9) Brent, R; Annu Rev Genet 1997, V31, P663 HCAPLUS
(10) Brent, R; Cell 1985, V43, P729 HCAPLUS
(11) Chardin, P; Science 1993, V260, P1338 HCAPLUS
(12) Chatoo, B; Genetics 1979, V93, P51
(13) Chien, C; Proc Natl Acad Sci U S A 1991, V88, P9578 HCAPLUS
(14) Colas, P; Nature 1996, V380, P548 HCAPLUS
(15) Dang, C; Mol Cell Biol 1991, V11, P954 HCAPLUS
(16) Dessens, A; Encyclopedie des Mots Historiques Vrais ou Faux 1980, P268
(17) Durfee, T; Genes Dev 1993, V7, P555 HCAPLUS
(18) Dyson, H; Biochemistry 1990, V29, P4129 HCAPLUS
(19) Ellington, A; Nature 1990, V346, P818 HCAPLUS
(20) Fagan, R; Cell 1994, V78, P799 HCAPLUS
(21) Fearon, E; Proc Natl Acad Sci U S A 1992, V89, P7958 HCAPLUS
(22) Fields, S; Nature 1989, V340, P245 HCAPLUS
(23) Finley, R; DNA Cloning, Expression Systems:A Practical Approach 1995, P169
(24) Finley, R; Proc Natl Acad Sci U S A 1994, V91, P12980 HCAPLUS
(25) Fromont-Racine, M; Nat Genet 1997, V16, P277 HCAPLUS
(26) Gold, L; Proc Natl Acad Sci U S A 1997, V94, P59 HCAPLUS
(27) Golemis, E; Mol Cell Biol 1992, V12, P3006 HCAPLUS
(28) Gyuris, J; Cell 1993, V75, P791 HCAPLUS
(29) Harper, J; Cell 1993, V75, P805 HCAPLUS
(30) James, P; Genetics 1996, V144, P1425 HCAPLUS
(31) Jiang, R; Genes Dev 1996, V10, P3105 HCAPLUS
(32) Katti, S; J Mol Biol 1990, V212, P167 HCAPLUS
(33) Kaufer, N; Nucleic Acids Res 1983, V11, P3123 MEDLINE
(34) Keegan, K; Oncogene 1996, V12, P1537 HCAPLUS
(35) Keegan, L; Science 1986, V231, P699 HCAPLUS
(36) Leanna, C; Nucleic Acids Res 1996, V24, P3341 HCAPLUS
(37) Licitra, E; Proc Natl Acad Sci U S A 1996, V93, P12817 HCAPLUS
(38) Lu, Z; Biotechnology 1995, V13, P366 HCAPLUS
(39) Ma, H; Gene 1987, V58, P201 HCAPLUS
(40) Ma, J; Cell 1988, V55, P443 HCAPLUS
(41) McNabb, D; Curr Opin Biotechnol 1996, V7, P554 HCAPLUS
(42) McQuade, T; Science 1990, V247, P454 HCAPLUS
(43) Mendelsohn, A; Curr Opin Biotechnol 1994, V5, P482 HCAPLUS
(44) Meroni, G; EMBO J 1997, V16, P2892 HCAPLUS
(45) Parks, L; Lipids 1995, V30, P227 HCAPLUS
(46) Scott, J; Curr Opin Biotechnol 1994, V5, P40 HCAPLUS
(47) Shih, H; Proc Natl Acad Sci U S A 1996, V93, P13896 HCAPLUS
(48) Strachan, T; Nat Genet 1997, V16, P126 HCAPLUS
(49) Thomas, B; Genes Dev 1997, V11, P1289 HCAPLUS
(50) Triezenberg, S; Genes Dev 1988, V2, P730 HCAPLUS
(51) Vasavada, H; Proc Natl Acad Sci U S A 1991, V88, P10686 HCAPLUS
(52) Vidal, M; Proc Natl Acad Sci U S A 1996, V93, P10315 HCAPLUS
(53) Vidal, M; Proc Natl Acad Sci U S A 1996, V93, P10321 HCAPLUS
(54) Vojtek, A; Cell 1993, V74, P205 HCAPLUS
(55) Wang, T; Science 1994, V265, P674 HCAPLUS
(56) Xu, C; Proc Natl Acad Sci U S A 1997, V94, P12473 HCAPLUS
(57) Yang, M; Nucleic Acids Res 1995, V23, P1152 HCAPLUS
(58) Zervos, A; Cell 1993, V72, P223 HCAPLUS
(59) Zhang, J; Anal Biochem 1996, V242, P68 HCAPLUS

```
=> => fil wpix
FILE 'WPIX' ENTERED AT 08:17:00 ON 26 OCT 2004
COPYRIGHT (C) 2004 THE THOMSON CORPORATION

FILE LAST UPDATED:            19 OCT 2004      <20041019/UP>
MOST RECENT DERWENT UPDATE:      200467         <200467/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE
```

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
PLEASE VISIT:
http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
http://thomsonderwent.com/coverage/latestupdates/ <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER
GUIDES, PLEASE VISIT:
http://thomsonderwent.com/support/userguides/ <<<

>>> NEW! FAST-ALERTING ACCESS TO NEWLY-PUBLISHED PATENT
DOCUMENTATION NOW AVAILABLE IN DERWENT WORLD PATENTS INDEX
FIRST VIEW - FILE WPIFV.
FOR FURTHER DETAILS: http://www.thomsonderwent.com/dwpifv <<<

>>> NEW DISPLAY FORMAT HITSTR ADDED ALLOWING DISPLAY OF
HIT STRUCTURES WITHIN THE BIBLIOGRAPHIC DOCUMENT <<<

>>> SMILES and ISOSMILES strings are no longer available as
Derwent Chemistry Resource display fields <<<

=> d l112 all abeq tech abex tot

L112 ANSWER 1 OF 9 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 2002-599413 [64] WPIX
DNC C2002-169246
TI Novel peptide comprising leukocyte antigen binding peptide of human CD45
polypeptide, useful for producing activated cytotoxic T lymphocytes, for
killing cancerous cells e.g. leukemia.
DC B04 D16
IN AMROLIA, P J; STAUSS, H J
PA (IMCO-N) IMPERIAL COLLEGE INNOVATIONS LTD
CYC 95
PI WO 2002044207 A1 20020606 (200264)* EN 56 C07K014-705
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM
DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC
LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE
SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001016472 A 20020611 (200264) C07K014-705
US 2003103946 A1 20030605 (200339) A61K048-00
EP 1339745 A1 20030903 (200365) EN C07K014-705
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
RO SE SI TR
ADT WO 2002044207 A1 WO 2000-GB4566 20001130; AU 2001016472 A WO 2000-GB4566
20001130, AU 2001-16472 20001130; US 2003103946 A1 US 2001-3983 20011031;
EP 1339745 A1 EP 2000-978987 20001130, WO 2000-GB4566 20001130
FDT AU 2001016472 A Based on WO 2002044207; EP 1339745 A1 Based on WO
2002044207
PRAI WO 2000-GB4566 20001130
IC ICM A61K048-00; C07K014-705
ICS A61K035-14; A61P037-02; C07H021-04; C07K007-06; C07K007-08;
C07K014-74; **C07K019-00**; C12N005-06; C12N005-08; C12N005-10;
C12N015-12; C12N015-62; **C12P021-02**; C12Q001-68
AB WO 200244207 A UPAB: 20021007
NOVELTY - A peptide (I) comprising the human leukocyte antigen
(HLA)-binding peptide of human CD45 polypeptide, its portion or variant,
provided that the peptide is not the intact human CD45 polypeptide, is
new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(1) a polypeptide fusion molecule (II) which comprises an HLA heavy

chain molecule joined via a flexible linker to an HLA-binding peptide of CD45 such that the HLA-binding peptide occupy the peptide-binding groove of the HLA molecule;

(2) a polynucleotide (III) encoding (I) or (II);

(3) an expression vector (IV) capable of expressing (I) or (II);

(4) a host cell (V) comprising (III) or (IV);

(5) preparation of (I);

(6) a kit (VI) of parts comprising (I) and an antigen presenting cell;

(7) an antigen-presenting cell (VII), where its major histocompatibility complex (MHC) Class I molecules are loaded with (I);

(8) an activated cytotoxic T lymphocyte (CTL) (VIII) obtained by contacting in vitro CTL with (VII), which selectively **recognize** a cell which expresses (I), or selectively **recognizes** a malignant cell which expresses CD45;

(9) a T-cell receptor (TCR) (IX) which **recognizes** a cell that expresses (I), obtained from (VIII), or a functionally equivalent molecule to TCR which **recognizes** a malignant hematopoietic cell which expresses CD45;

(10) a polynucleotide (X) encoding (IX);

(11) an expression vector capable of expressing (IX);

(12) treating (M1) a patient with a hematopoietic malignancy comprising:

(a) detecting a HLA-binding peptide of human CD45 (the type of class I MHC molecule which binds the peptide in the patient) and/or determining for a given class I MHC molecule of the patient which peptide (or peptides) of human CD45 binds the class I MHC molecule in the patient;

(b) providing an activated CTL which is allogenic (allorestricted) with respect to the Class I MHC molecule which binds the peptide in the patient and the CTL is specific for the peptide;

(c) undertaking a stem cell transplantation of the patient from a donor who is negative for the type of class I MHC molecule, which, in the patient, binds the peptide; and

(d) administering the activated CTL to the patient;

(13) a library of activated CTL, where each member of the library **recognizes** a CD45 peptide when presented by a particular, recorded HLA and has its HLA haplotype recorded;

(14) a library of HLA-binding peptides of human CD45 polypeptide, where for each member of the library the type of HLA molecule it binds is recorded; and

(15) a library of antigen presenting cells each loaded with an HLA-binding peptide of human CD45 polypeptide, where for each member of the library the identity of the peptide is recorded and, optionally, the HLA haplotype of the antigen presenting cell.

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - Inhibitor of colony forming unit-granulocyte macrophage (CFU-GM) colony formation; immunotherapy.

Three p1218 specific CTL lines showed potent cytotoxicity against HLA A2 +ve (C1RA2) but not A -ve (WS29 or K562) hematopoietic cell lines, although some alloreactivity against A2+ve, non-hematopoietic **targets** was observed. p1218 line 2, had the highest avidity in peptide titration assays, showed significant cytotoxicity against PGMN in 4/5HLA A2+ve patients with chronic myeloid leukemia (CML), including 1 in myeloid blast crisis, but 0/4 HLA A2 -ve normal controls.

Treatment of CD34+ve PBMN/BMMN with p1218 specific CTL inhibited CFU-GM colony formation by greater than 90% in 4/5 HLA A2+ve CML patients without significant inhibition in 5/5 HLA A2-ve normal controls, demonstrated that the p1218-specific CTL had potent activity against leukemic progenitors.

USE - (VII) Is useful for producing activated CTL in vitro which involves contacting in vitro CTL with (VII) for a period of time sufficient to activate, in an antigen specific manner, where the CTL and the antigen presenting cell are allogenic with respect to the class I MHC

molecule that is presenting peptides of CD45. The antigen is loaded on Class I MHC molecules expressed on the surface of a suitable antigen-presenting cell by contacting a sufficient amount of the antigen with an antigen-presenting cell, where before contact the class I MHC molecules of the antigen-presenting cell are substantially unoccupied and after contacting the class I MHC molecules are substantially fully occupied. The antigen-presenting cell comprises (IV).

(VIII) Is useful for killing **target** cells expressing (I) in a patient. (VIII) or CTL expressing (X) is useful in the manufacture of a medicament for killing **target** cells expressing (I) in a patient. (X) is useful for killing **target** cells (cancer cells) expressing (I) in a patient which involves obtaining CTL from the patient, introducing into CTL (X), and introducing the cells thus produced into the patient undergone an allogenic stem cell transplantation. The cancer is leukemia which expresses the CD45 polypeptide. M1 is useful for treating a patient with hematopoietic malignancy (all claimed).

(I) Is useful for generating peptide-specific CTL, in particular useful in immunotherapeutic methods to **target** and kill cells which express the CD45 polypeptide. (I) when bound to HLA-A0201, is useful for eliciting production of a CTL which **recognizes** a cell which expresses (I).

(V) Is useful for preparing (I) or (II). (VIII) is useful for killing **target** cells such as malignant and hematopoietic cells.

ADVANTAGE - (VIII) destroys the malignant hematopoietic cells but not the transplanted cells.

Dwg.0/5

FS CPI

FA AB; DCN

MC CPI: B04-C01B; B04-E03D; B04-E03H; B04-E08; B04-F0100E; B04-F02; B04-F07A0E; B04-K01; B04-N08; B11-C08E; B12-K04E; B12-K04F; B14-H01; D05-H08; D05-H09; D05-H12A; D05-H12E; D05-H14; D05-H14B1; D05-H17A4

TECH UPTX: 20021007

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preparation: Preparation of (I) involves culturing (V) and obtaining the peptide from the host cell or its culture medium (claimed).

Preferred Peptide: (I) Is capable of binding to HLA-A0201. The peptide-bound HLA-A0201 is capable of eliciting the production of CTL which **recognizes** a cell which expresses a polypeptide comprising a sequence (S1) of FLYDVIAST, ALIAFLAFL, KLFTAKLNV, MIWEQKATV, NLSELHPYL, VNLSELHPYL, LLAFGFAFL, YLYNKETKL, LILDVPPGV, TLILDVPPGV, ILYNNHKFT, ILPYDYNRV, YILIHQALV, FQLHDCTQV, KLLAFGFAFL or YQYQYTNWSV. The peptide has non-peptide bonds.

Preferred Polynucleotide: (II) Is DNA.

Preferred Cell: In (VII), the antigen presenting cell is a cell defective in, or lacks, the expression of TAP peptide transporter. The cell is a T2 cell, an RAM-S cell or a Drosophila cell.

Preferred Method: In M1, the type of Class I MHC molecule is determined by DNA analysis and the activated CTLs are selected from a library of CTL.

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) Is also synthesized by the Fmoc-polyamide mode of solid-phase peptide synthesis.

ABEX UPTX: 20021007

WIDER DISCLOSURE - Also disclosed are:

(a) a composition comprising (I); and

(b) a pharmaceutical composition comprising (VIII).

SPECIFIC PEPTIDES - (I) Comprises or consists of the amino acid sequence FLYDVIAST, ALIAFLAFL, KLFTAKLNV, MIWEQKATV, NLSELHPYL, VNLSELHPYL, LLAFGFAFL, YLYNKETKL, LILDVPPGV, TLILDVPPGV, ILYNNHKFT, ILPYDYNRV, YILIHQALV, FQLHDCTQV, KLLAFGFAFL or YQYQYTNWSV, its portion or variant (claimed).

ADMINISTRATION - (VIII) Is administered at a dose of 108-1011, most preferably 109-1010. Administration routes not specified.

EXAMPLE - Production of activated cytotoxic lymphocytes (CTL) using Class I molecules and the CD45 peptide antigen FLYDVIAST and their administration, was carried out as follows. Activated CTL were produced using human leukocyte antigen (HLA)-A2 class I molecules and the nonamer peptide from CD45: FLYDVIAST.
Cells with an endogenous defect in the peptide loading of HLA class I molecules were used as stimulator cells e.g., human T2 cells, murine RMA-S/A2 cells or Drosophila cells transfected with human HLA-A0201, B7.1 and **intercellular** adhesion molecule (ICAM)-1. The HLA-A0201 molecules expressed in these cells were loaded with exogenously supplied peptides. The peptide was synthesized on an Applied Biosystems synthesizer, and subsequently purified by high performance liquid chromatography (HPLC). The culture of stimulator cells were maintained in an appropriate medium to optimize the in vitro conditions for the generation of specific cytotoxic T cells.
Prior to incubation of the stimulator cells with the cells to be activated, e.g., precursor CD8 cells, an amount of antigenic peptide was added to the stimulator cell culture, of sufficient quantity to become loaded onto human Class I molecules to be expressed on the surface of the stimulator cells. Resting or precursor CD8 cells were then incubated in culture with the appropriate stimulator cells for a time period sufficient to activate the CD8 cells.
Therefore the CD8 cells were activated in an antigen-specific manner. The ratio of resting or precursor CD8 (effector) cells to stimulator cells varied from individual to individual and further depend upon variables such as amenability of an individual's lymphocytes to culturing conditions. The lymphocyte:stimulator cell (Drosophila cell) ratio was typically in the range of 2:1 to 100:1, e.g., 3x107 human PBL and 3x106 live Drosophila cells were admixed and maintained in 20 ml of RPMI 1640 culture medium. The effector/stimulator culture were maintained for as long a time to stimulate CD8 cells to isolate peptide-specific CTL lines. Effective, cytotoxic amounts of the activated CD8 cells range between 1x106 and 1x1012 for killing **target** cells in patients suffering from cancer.

```
L112 ANSWER 2 OF 9  WPIX  COPYRIGHT 2004 THE THOMSON CORP on STN
AN   2002-418829 [45]   WPIX
DNC  C2002-118325
TI   Process for specifically modulating the properties of an
     intracellular target molecule used for the treatment of
     various disorders.
DC   B04 D16
IN   BRENT, R; COHEN, B A; COLAS, P
PA   (CNRS) CENT NAT RECH SCI; (MASS-N) MASSACHUSETTS GEN HOSPITAL; (MOLE-N)
     MOLECULAR SCI INST; (BREN-I) BRENT R; (COHE-I) COHEN B A; (COLA-I) COLAS P
CYC  99
PI   EP 1205191       A1 20020515 (200245)* EN    33    A61K047-48
        R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
           RO SE SI TR
     WO 2002055108    A1 20020718 (200257)  EN          A61K047-48
       RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
           NL OA PT SD SE SL SZ TR TZ UG ZW
        W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
           DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
           KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
           RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
     US 2003143626    A1 20030731 (200354)              A61K048-00     <--
     EP 1345627       A1 20030924 (200363)  EN          A61K047-48
        R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
           RO SE SI TR
     AU 2002219153    A1 20020724 (200427)              A61K047-48
     JP 2004516848    W  20040610 (200438)       254    C12N015-09
```

ADT EP 1205191 A1 **EP 2000-403156 20001113**; WO 2002055108 A1 WO 2001-EP14199 20011113; US 2003143626 A1 **US 2001-66965 20011113**; EP 1345627 A1 EP 2001-273076 20011113, WO 2001-EP14199 20011113; AU 2002219153 A1 AU 2002-219153 20011113; JP 2004516848 W WO 2001-EP14199 20011113, JP 2002-555840 20011113

FDT EP 1345627 A1 Based on WO 2002055108; AU 2002219153 A1 Based on WO 2002055108; JP 2004516848 W Based on WO 2002055108

PRAI **EP 2000-403156 20001113**

IC ICM A61K047-48; A61K048-00; C12N015-09
ICS A61K031-7052; A61K038-00; A61K038-08; A61K038-17; A61P001-02; A61P003-00; A61P009-10; A61P017-00; A61P021-00; A61P025-00; A61P031-04; A61P031-10; A61P031-12; A61P035-00; A61P037-02; C07H021-04; C07K007-08; C07K014-47; **C07K019-00**; C12N001-15; C12N001-19; C12N001-21; C12N005-06; C12N005-10; **C12P021-02**; G01N033-15; G01N033-50; G01N033-53

AB EP 1205191 A UPAB: 20020717

NOVELTY - Process for specifically modulating the properties of an **intracellular target** molecule T, and/or of a cellular component C which interacts directly or indirectly in a cell with T.

DETAILED DESCRIPTION - Process for specifically modulating the properties of an **intracellular target** molecule T, and/or of a cellular component C which interacts directly or indirectly in a cell with T, comprising:

(a) introducing into a cell a chimeric molecule, a so-called **targeted** effector, comprising:

(i) a **recognition** moiety R having the capacity to specifically interact within the cell, with a site on an **intracellular target** molecule T, R interacting with T with a first affinity A1; and

(ii) an effector moiety, E covalently linked to the **recognition** moiety R, E being a molecule or portion which has an initial capacity to exert an effect on at least one molecule M, and which when it is covalently linked to R, acquires the capacity to specifically exert on the **intracellular target** molecule, T.

INDEPENDENT CLAIMS are also included for the following:

(1) process for the production of a **targeted** effector having the capacity to specifically modulate the properties of an **intracellular target** molecule T, and/or a cellular component C which interacts directly or indirectly in a cell with T comprising:

(i) production of a random pool of peptides, so called **recognition** moieties R;

(ii) screening of the random pool produced in (i) against T in a cell, in conditions suitable to allow identification of **recognition** moieties R capable of interacting with T;

(iii) optionally contacting the moieties selected in (ii) with proteins other than T to determine the specificity range of each of said moieties, and to identify moieties having a desired specificity range;

(iv) covalent linkage of the **recognition** moieties R to an effector moiety E, E being a molecule which initially has the capacity to exert a predetermined effect on at least one **intracellular** component M.;

(v) verification of the affinity A1 with which the **recognition** moiety R interacts with T, or of the affinity A2 with which the **targeted** effector, interacts with T;

(vi) if both of A1 and A2 correspond to Kd values greater than 1 x 10-8M, alteration of the binding region of the effector moiety to adjust the binding affinity of the interaction between T and the selected moiety so that the Kd becomes less than 1 x 10-8M;

(2) process for conferring on an effector moiety E the ability to specifically modulate the properties of an **intracellular** protein T, or an **intracellular** component which interacts directly or indirectly with T, comprising:

(i) covalently linking the effector moiety E to a **recognition** moiety R where R comprises a molecule having the capacity to specifically interact within a cell with a site on an **intracellular target** molecule T, the interaction with T occurring with an affinity A1 which corresponds to a Kd value of less than 1 x 10-8M and E being a molecule which has an initial capacity to exert the effect on the **intracellular target** molecule T; and

(ii) optionally optimizing the affinity of the interaction between T and R by altering the chemical composition of the binding region of R to provide an affinity in the desired range;

(3) chimeric molecule, so called **targeted** effector comprising:

(i) a **recognition** moiety R having the capacity to specifically interact within a cell with a site on an **intracellular target** molecule T the interaction with T occurring with an affinity A1; and

(ii) an effector moiety E, covalently linked to R, E being a molecule which has an initial capacity to exert an effect on at least one molecule M, and which when it is covalently linked to R, acquires the capacity to specifically exert the effect on the **intracellular target** molecule T;

(4) nucleic acid encoding a chimeric protein operably linked to regulatory sequences for expression in a eukaryotic cell;

(5) vector capable of stably introducing a nucleic acid into a prokaryotic or eukaryotic cell;

(6) pharmaceutical composition comprising a chimeric molecule, or a nucleic acid in association with a pharmaceutically acceptable excipient; and

(7) an **intracellular recognition** molecule R, composed of a conformationally constrained **recognition** domain, displayed in a platform.

ACTIVITY - Antimicrobial; Immunomodulatory; Nootropic; Neuroprotective; Metabolic; Neuroleptic; Cytostatic; Cardiant.

MECHANISM OF ACTION - None given in the specification.

USE - The chimeric protein or nucleic acid is used in the preparation of a medicament for the treatment of microbial infections, immunological disorders, neurological disorders, metabolic disorders, psychiatric disorders, myopathies, genetic disorders, cancer, cardiovascular disorders and dental disorders (claimed).

Dwg.0/7

FS CPI

FA AB; DCN

MC CPI: B04-E08; B04-N04; B11-C07B; B12-K04E; B14-A01; B14-F01; B14-G03; B14-H01; B14-H01B; B14-J01; B14-J01B3; B14-L06; B14-N03; B14-N06; B14-S03A; D05-H10; D05-H12A; D05-H12E

TECH UPTX: 20020717

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Process: The binding affinity A1 corresponds to a Kd between 1 x 10 to the power -9M and 1 x 10 to the power -12M. R is a mutant of a parent **recognition** moiety Ra which has the capacity to specifically interact with a site on the **intracellular target** molecule T, the interaction between Ra and T occurring with an affinity A3, where the Kd corresponding to A3 is greater than the Kd corresponding to A1. E has the initial capacity to exert an effect in cis and/or in trans on M and when it is covalently bound to R, acquires the capacity to exert the effect in trans on T. The moiety R contains a conformationally constrained variable region displayed from a platform which is **thioredoxin** (**TRX**) or a **TRX**-like protein and the constrained region is a peptide 5-60 amino acids preferably 10-40 amino acids. The effect exerted by the effector moiety E involves a change in the chemical, biochemical,physical and/or functional properties of T and/ or C and where E comprises an enzyme, co-factor, an addressing signal, a transcription regulatory protein, a tracer protein, a molecule having therapeutic or diagnostic

properties, a second **recognition** moiety, a second **targeted** effector, a radionuclide or chemical modifier. T is a protein, a nucleic acid, a carbohydrate, a phosphorylated molecule, a lipid or a combination but more preferably T is a protein comprising at least 2 functionally distinct domains Ta and Tb, and where R specifically binds to Ta and E specifically binds to Tb. The **targeted** effector is introduced into the cell by expression of a DNA sequence encoding the **targeted** effector as a fusion protein, or in a purified form using a cell permeable agent such as a protein transduction domain.

ABEX UPTX: 20020717
EXAMPLE - No suitable data is given in the specification.

L112 ANSWER 3 OF 9 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 2002-217182 [27] WPIX
DNC C2002-066484
TI New soluble cytokine receptor which binds interleukin-T-cell inducible factor and antagonizes its activity in inflammatory and immune diseases such as cancer, diabetes, asthma, sepsis, psoriasis and autoimmune diseases.
DC B04 D16
IN KINDSVOGEL, W R; TOPOUZIS, S
PA (ZYMO) ZYMOGENETICS INC; (KIND-I) KINDSVOGEL W R; (TOPO-I) TOPOUZIS S
CYC 97
PI WO 2002012345 A2 20020214 (200227)* EN 117 C07K014-705
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001090524 A 20020218 (200244) C07K014-705
US 2003157096 A1 20030821 (200356) A61K039-395
EP 1337636 A2 20030827 (200357) EN C12N015-12
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
JP 2004505641 W 20040226 (200416) 190 C12N015-09
ADT WO 2002012345 A2 WO 2001-US24838 20010808; AU 2001090524 A AU 2001-90524 20010808; US 2003157096 A1 Provisional US 2000-223827P 20000808, Provisional US 2000-250876P 20001201, US 2001-925055 20010808; EP 1337636 A2 EP 2001-970531 20010808, WO 2001-US24838 20010808; JP 2004505641 W WO 2001-US24838 20010808, JP 2002-518316 20010808
FDT AU 2001090524 A Based on WO 2002012345; EP 1337636 A2 Based on WO 2002012345; JP 2004505641 W Based on WO 2002012345
PRAI US 2000-250876P 20001201; US 2000-223827P 20000808; US 2001-925055 20010808
IC ICM A61K039-395; C07K014-705; C12N015-09; C12N015-12
ICS A61K038-00; A61K038-17; A61P029-00; A61P037-00; A61P037-02; A61P037-06; C07H021-04; C07K014-715; C07K016-28; **C07K019-00** ; C12N001-15; C12N001-19; C12N001-21; C12N005-06; C12N005-10; C12N015-62; **C12P021-02**
AB WO 200212345 A UPAB: 20020429
NOVELTY - An isolated soluble cytokine receptor polypeptide (I), designated zcytor11 comprising a sequence (S1) of 211 amino acids defined in the specification or a sequence 90% identical to (S1) and which binds interleukin-T-cell inducible factor (IL-TIF) or antagonizes IL-TIF activity, where (I) forms homodimeric, heterodimeric or multimeric receptor complex, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an isolated polynucleotide (II) that encodes (I), where the polypeptide encoded by the polynucleotide sequence binds or antagonizes IL-TIF having a sequence of 179 amino acids defined in the specification;

(2) an expression vector (III) comprising operably linked a transcription promoter, a first DNA segments encoding (I) and a transcription terminator; and a second transcription promoter, a second DNA segment encoding a soluble class I or class II cytokine receptor polypeptide, and a transcription terminator, where the first and second DNA segments are contained within a single expression vector or are contained within independent expression vectors;

(3) a culture cell (IV) comprising (III), and which expresses the polypeptides encoded by the DNA segments;

(4) a DNA construct (V) encoding a fusion protein comprising a first DNA segment encoding (I), and at least one other DNA segment encoding a soluble class I or class II cytokine receptor polypeptide, where the first and second other DNA segments are connected-in-frame and encode the fusion protein;

(5) an expression vector comprising a transcription promoter, (V) and a transcription terminator, where the promoter is operably linked to the DNA construct which is linked to the transcription terminator;

(6) a cultured cell (VI) comprising the above vector;

(7) an isolated heterodimeric or multimeric soluble receptor complex, comprising soluble receptor subunits comprising (I);

(8) producing (I); and

(9) an antibody produced by using (I) which specifically binds to a homodimeric, heterodimeric or multimeric receptor complex comprising a soluble cytokine receptor polypeptide.

ACTIVITY - Antidiabetic; Antiinflammatory; Cytostatic; Antithyroid; Immunosuppressive; Antibacterial; Antiasthmatic; Antipsoriatic; Neuroprotective; Dermatological; Antirheumatic; Antiarthritic; Antiallergic. No supporting data is given.

MECHANISM OF ACTION - Antagonist of IL-TIF.

USE - (I) is useful for reducing IL-TIF- or IL-9 induced inflammation, and inhibiting IL-TIF-induced proliferation of hematopoietic cells and their progenitors, especially lymphoid cells such as macrophages or T cells, by culturing bone marrow or peripheral blood cells with a composition comprising (I) to reduce proliferation of the hematopoietic cells in the bone marrow or peripheral blood cells as compared to bone marrow or peripheral blood cells cultured in the absence of soluble cytokine receptor. (I) is also useful for suppressing an immune response in a mammal exposed to an antigen or pathogen, by determining a level of an antigen- or pathogen-specific antibody, administering a composition comprising (I), determining a post administration level of antigen- or pathogen-specific antibody, and comparing the level of antibody before administration to the level of antibody after administration, where a lack of increase or a decrease in antibody level is indicative of suppressing an immune response. (I) is further useful for producing an antibody to soluble cytokine receptor polypeptide. (VI) is useful for producing a fusion protein (claimed). Soluble zcytor11 receptor or heterodimeric polypeptide is useful for enhancing the in vivo killing of **target** tissues by directly stimulating a zcytor11 receptor-modulated apoptotic pathway, resulting in cell death of hyperproliferative cells expressing zcytor11 receptor or a zcytor11 heterodimeric receptor, such as soluble zcytor11/CRF2-4 receptor. IL-TIF is involved in promoting Th1-type immune responses and antagonist of IL-TIF have beneficial use against diseases involving such immune responses. (I) is useful as cytokine antagonist and for detecting ligands that stimulate the proliferation and/or development of hematopoietic, lymphoid and myeloid cells in vitro and in vivo. Soluble zcytor11 heterodimers are useful as antagonists in inflammatory and immune diseases or conditions such as pancreatitis, type I diabetes (IDDM), pancreatic cancer, Graves disease, inflammatory bowel disease (IBD), Crohn's disease, colon and intestinal cancer, diverticulosis, autoimmune disease, sepsis, asthma, end-stage renal disease, psoriasis, organ or bone marrow transplant and kidney dysfunction. Soluble zcytor11 receptor or heterodimeric receptor polypeptides are useful in vivo or in diagnostic applications to detect IL-TIF expressing cancers in vivo or in tissue

samples and to prepare antibodies. Antibodies **recognizing** zcytoR11, soluble zcytoR11/CRF2-4 heterodimers, and multimers are useful to antagonize or agonize signaling by the IL-TIF receptors in the treatment of autoimmune disease such as IDDM, multiple sclerosis (MS), systemic lupus erythematosus (SLE), myasthenia gravis, rheumatoid arthritis and IBD. Anti-soluble zcytor11, anti-soluble zcytoR11/CRF2-4 heterodimer or multimer monoclonal antibody (MAb) is useful as an antagonist to deplete unwanted immune cells to treat autoimmune disease such asthma, allergy and other atopic disease. ZcytoR11 serves as a **target** for MAb therapy of cancer where an antagonizing MAb inhibits cancer growth and **targets** immune-mediated killing. Antibodies to soluble zcytor11 receptor or heterodimeric polypeptide are useful for tagging cells that express the corresponding receptors and assaying their expression levels, for affinity purification, within diagnostic assays for determining circulating levels of soluble receptor polypeptides, for detecting or quantitating soluble zcytor11 receptor or soluble zcytor11 heterodimeric polypeptide and as neutralizing antibodies or as antagonists to block zcytor11 receptor or zcytor11 heterodimeric polypeptide such as zcytor11/CRF2-4 or IL-TIF activity in vitro and in vivo.
Dwg.0/0

FS CPI
FA AB; DCN
MC CPI: B04-E03D; B04-E03H; B04-E08; B04-F0100E; B04-G04; B04-K01K0E; B04-N08; B14-C03; B14-C09B; B14-E10C; B14-G02; B14-H01; B14-J05; B14-K01A; B14-N10; B14-N17; B14-S04; B14-S06; D05-H11; D05-H12A; D05-H12C; D05-H12E; D05-H14; D05-H17A4; D05-H17C

TECH UPTX: 20020429

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preparation: (I) is produced by culturing (IV) and isolating the soluble receptor polypeptide produced by the cell. The antibody is produced by inoculating an animal with (I) and isolating the antibody.
Preferred Polypeptide: (I) forms a homodimeric, heterodimeric or multimeric receptor complex and further comprises a soluble class I or class II cytokine receptor. The soluble cytokine receptor further comprises a soluble class I or class II cytokine receptor, or a soluble cytokine receptor family (CRF)2-4 receptor polypeptide, IL-10 receptor polypeptide or DIRS1 (undefined) receptor polypeptide having a sequence of 199, 211 and 201 amino acids, respectively defined in the specification, and also comprises affinity tag, chemical moiety, toxin or label. The polypeptide further encodes an **intracellular** domain.
Preferred Vector: (III) further comprises a secretory signal sequence operably linked to the first and second DNA segments.
Preferred Cell: In (IV), the first and second DNA segments are located at independent expression vectors and are cotransfected into the cell.

ABEX UPTX: 20020429

WIDER DISCLOSURE - Also disclosed are orthologs of (II).

EXAMPLE - An expression vector was prepared for the expression of the soluble, extracellular domain of the zcytor11 polypeptide. The construct pC4zcytor11CEE, was designed to express a zcytor11 polypeptide comprised of the predicted initiating methionine and truncated adjacent to the predicted transmembrane domain, and with a C-terminal Glu-Glu tag. A zcytor11 DNA fragment comprising the zcytor11 extracellular cytokine binding domain was created using polymerase chain reaction (PCR), and purified. The excised DNA was subcloned into a plasmid expression vector having a signal peptide, and attached a Glu-Glu tag to the C-terminus of the zcytor11 polypeptide-encoding polynucleotide sequence. Restriction digested zcytor11 insert and previously digested vector were ligated and electroporated into competent cells such as DH10B competent cells and plated onto LB plates containing 50 mg/ml ampicillin, and incubated overnight. Colonies were screened by restriction analysis of DNA prepared from individual colonies. The insert sequence of positive clones was

verified by sequence analysis.

L112 ANSWER 4 OF 9 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 2002-130791 [17] WPIX
CR 2003-352713 [33]
DNC C2002-040195
TI New polypeptide comprising an enterokinase **recognition** sequence for isolating and purifying a protein of interest or its fragment.
DC B04 D16
IN LADNER, R C; LEY, A C; LUNEAU, C J
PA (DYAX-N) DYAX CORP
CYC 95
PI WO 2001098366 A2 20011227 (200217)* EN 119 C07K007-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001068559 A 20020102 (200230) C07K007-00
EP 1326882 A2 20030716 (200347) EN C07K007-06
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
JP 2004503219 W 20040205 (200412) 173 C12N015-09
ADT WO 2001098366 A2 WO 2001-US19539 20010619; AU 2001068559 A AU 2001-68559 20010619; EP 1326882 A2 EP 2001-946519 20010619, WO 2001-US19539 20010619; JP 2004503219 W WO 2001-US19539 20010619, JP 2002-504321 20010619
FDT AU 2001068559 A Based on WO 2001098366; EP 1326882 A2 Based on WO 2001098366; JP 2004503219 W Based on WO 2001098366
PRAI US 2000-597321 20000619
IC ICM C07K007-00; C07K007-06; C12N015-09
ICS C07K014-00; **C07K019-00**; C12N001-15; C12N001-19; C12N001-21; C12N005-10; C12N009-50; C12N015-10; C12N015-11; C12N015-62; **C12P021-02**; C12Q001-02; C12Q001-48; C12Q001-68; G01N033-53; G01N033-566
AB WO 200198366 A UPAB: 20040218
NOVELTY - A polypeptide (I) comprising an enterokinase **recognition** sequence (S1) selected from any one of the 182 amino acids sequences, given in the specification, and having the formula (F1) or (F2), is new.

DETAILED DESCRIPTION - A new polypeptide (I) comprises an enterokinase **recognition** sequence (S1) selected from any one of the 182 amino acids sequences, given in the specification, and has the formula (F1) or (F2)..

Z1-(Xaa)1-4-Asp-Arg-Xaa5-Z2 (F1)

Xaa1 = an optional amino acid residue, which, if present, is Ala, Asp, Glu, Phe, Gly, Ile, Asn, Ser or Val;

Xaa2 = an optional amino acid residue which, if present, is Ala, Asp, Glu, His, Ile, Leu, Met, Gln or Ser;

Xaa3 = an optional amino acid residue which, if present, is Asp, Glu, Phe, His, Ile, Met, Asn, Pro, Val or Trp;

Xaa4 = Ala, Asp, Glu or Thr;

Xaa5 = any amino acid residue;

Z1 and Z2 = optional and are, independently, polypeptides of one or more amino acids.

Z1-(Xaa)1-4-Glu-Arg-Xaa5-Z2 (F2)

Xaa1 = optional amino acid residue which, if present, is Asp or Glu;

Xaa2 = optional amino acid residue which, if present, is Val;

Xaa3 = an optional amino acid residue which, if present, is Tyr;

Xaa4 = an optional amino acid residue which, if present, is Asp, Glu or Ser; and

Xaa5 = any amino acid residue; and

Z1 and Z2 = optional and are, independently, polypeptides of one or more amino acids.

INDEPENDENT CLAIMS are also included for the following:

(1) a polynucleotide (II) encoding an enterokinase cleavable fusion protein including a ligand **recognition** sequence, an enterokinase **recognition** sequence (S1 or S2) and a protein of interest, in the direction of amino-terminus to carboxy-terminus;

(2) a vector (III) comprising circular DNA and including (II);

(3) an expression vector (IIIa) comprising (II) operably linked to a promoter sequence for expression in a recombinant host cell;

(4) a host cell (IV) transformed with (III) or (IIIa);

(5) isolating (M1) a protein of interest, by:

(a) culturing a recombinant host cell expressing (II), under conditions suitable for expression of the fusion protein;

(b) contacting the expressed fusion protein with a binding ligand immobilized on a solid support under conditions suitable for formation of a binding complex between the binding ligand and the ligand **recognition** sequence;

(c) contacting the binding complex with enterokinase; and

(d) recovering the protein of interest;

(6) isolating (M2) a genetic package of interest, by:

(a) expressing in a genetic package a fusion protein comprising a protein of interest fused to S1 which is fused to a polypeptide expressed on the surface of the genetic package;

(b) contacting the genetic package with a ligand for the protein of interest, which ligand is capable of being immobilized on a solid support, under conditions suitable for the formation of a binding complex between the ligand and the protein of interest;

(c) immobilizing the ligand on a solid support, either before or after (b);

(d) contacting the immobilized binding complex with enterokinase; and

(e) recovering the genetic package of interest from the solid support;

(7) controlling (M3) the activity of a protein of interest, by:

(a) expressing in a recombinant host a fusion protein comprising a first protein fused to S1 which is fused to a second protein, where the fusion protein has suppressed activity due to the conformation of elements; and

(b) treating the fusion protein with enterokinase so that the first protein and second protein are separated and at least one of the first protein and the second protein exhibits the activity of a protein of interest;

(8) detecting (M4) the expression of a fusion protein on the surface of a recombinant host, by:

(a) expressing, in a recombinant host, a fusion protein comprising a first protein fused to S1 which is fused to a second protein fused to a polypeptide expressed on the surface of the host;

(b) contacting the host with a ligand for the first protein immobilized on a solid support under conditions suitable for forming a binding complex between the ligand and the first protein;

(c) removing unbound materials;

(d) treating any bound complex with enterokinase;

(e) recovering hosts released from the support, where the recovered hosts are verified expressors of the fusion protein; and

(9) selecting display polypeptides from a display library that have specific (M5) affinity for a target, by:

(a) providing a display library of polypeptides comprising a multiplicity of genetic packages, where each genetic package expresses a fusion protein that comprises S1 between a display polypeptide library member and a polypeptide that anchors the fusion protein to the genetic package;

(b) contacting the display library with a target;

(c) immobilizing the target on a solid support, either before or after (b);

(d) separating non-binding genetic packages from bound genetic

packages;
(e) treating the bound genetic packages with enterokinase; and
(f) recovering and amplifying the genetic packages released.
Asp Ile Asn Asp Asp Arg (S1)
Gly Asn Tyr Thr Asp Arg (S2)
USE - The enterokinse recognition sequence of (I) is useful for isolating and purifying a protein of interest or its fragment (claimed).
ADVANTAGE - The enterokinase recognition sequences are highly specific and can be rapidly cleaved.
Dwg.0/2

FS CPI
FA AB; DCN
MC CPI: B04-C01; B04-E03H; B04-E08; B04-F0100E; B04-G01; B04-L04; B04-L05C; B04-N04; B04-N04A; B04-N04A0E; B04-N08; B11-B; B11-C08E6; B12-K04E; D05-C12; D05-H09; D05-H10; D05-H11; D05-H12A; D05-H12E; D05-H14; D05-H17A6

TECH UPTX: 20021031
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) is preferably prepared using solid phase synthesis.
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preparation: (I) may be prepared by standard recombinant techniques.
Preferred Peptide: In F1, Xaa1 is Asp, Xaa2 is Ile, Xaa3 is Asn, Xaa4 is Asp and Xaa5 is Met, Thr, Ser, Ala, Asp, Leu, Phe, Asn, Trp, Ile, Gln, Glu, His, Val, Gly or Tyr. Z1 is a ligand **recognition** sequence or a streptavidin binding domain selected from (S3 - S7) and tandemly arranged combinations or repeats. Z2 or Xaa5-Z2 is a protein of interest.
Preferred Vector: (IIIa) further comprises a signal sequence operably linked to the polynucleotide for effecting secretion of the expressed fusion protein into a culture medium.
Preferred Method: In M1, the fusion protein is not secreted on expression, of lyzing the host cell, and separating the cellular debris from the culture medium. The fusion protein is secreted on expression, after collecting culture media containing the secreted fusion protein. The fusion protein has the formula F1 or F2, where Z1 is a polypeptide comprising a sequence (S8). In M2, the ligand is biotinylated and the immobilization is by binding to immobilized streptavidin or avidin. The ligand is immobilized by binding to an immobilized antibody that binds the ligand. M2 further involves washing the support to remove unbound materials. The protein of interest is an antibody or its fragment. The genetic package is selected from bacteriophage, bacteria, bacterial spores, yeast cells, yeast spores, insect cells, eukaryotic viruses and mammalian cells, and is amplified after recovery in a host selected from bacterial, insect and mammalian cells, and yeast. The genetic package is a filamentous bacteriophage and the polypeptide expressed on the surface of the host is selected from gene (III) protein (comprising a sequence of 424 amino acids, given in the specification), domain 2::domain 3::transmembrane domain::**intracellular** domain of gene III protein (comprising a sequence of 319 amino acids, given in the specification), and domain 3::transmembrane domain::**intracellular** anchor of gene III protein (comprising a sequence of 150 amino acids, given in the specification). The genetic package is an M13 phage. In M3, the second protein is the protein of interest, e.g. protease, and the first protein is its inhibitor, or vice versa. The first protein is the variable light (VL) domain of an scFv antibody, and the second protein is the variable heavy (VH) domain of an scFv antibody, where the protein of interest is the scFv formed by the association of the first protein with the second protein, or vice versa. In M4, the second protein is an antibody or antibody fragment. The first protein is a streptavidin-binding polypeptide and the ligand is streptavidin. In M5, the display polypeptides comprise human Fabs and peptides of 10 - 21 amino acids in length, where each peptide contains two cysteines.
His Pro Gln Phe (S3)
Cys His Pro Gln Phe Cys (S4)

Cys His Pro Gln Phe Cys Ser Trp Arg (S5)
Trp His Pro Gln Phe Ser Ser (S6)
Pro Cys His Pro Gln Phe Pro Arg Cys Tyr (S7)
His Pro Gln Phe Ser Ser Pro Ser Ala Ser Arg Pro Ser Glu Gly Pro Cys His Pro Gln Phe Pro Arg Cys Tyr Ile Glu Asn Leu Asp Glu Phe Ser Gly Leu Thr Asn Ile (S8)

ABEX UPTX: 20021031

EXAMPLE - A phage display library was designed for the display of an exogenous polypeptide at the N-terminus of M13 phage gene III protein. The exogenous polypeptide was an 86-mer fusion protein having tandem ligand **recognition** sequences, a variegated segment of thirteen amino acids serving as a template for potential enterokinase (EK) **recognition** sequences, a factor Xa cleavage site, segments linking the foregoing domains and linking to the N-terminus of gene III protein. The exogenous display polypeptide comprised a sequence of 86 amino acids, given in the specification, where any amino acid residue except cysteine was permitted at each X position. The polypeptide comprise, from N-terminal to C-terminal, a linear streptavidin binding sequence, a constrained streptavidin binding loop, and a factor Xa cleavage site, respectively. The design gave a potential diversity of 4.2 x 10 to the power of 16. Approximately 2 x 10 to the power of 8 different display polypeptides were included in the library for screening. Phage were screened for a total of five rounds. In each screening round, two aliquots of phage were allowed to bind streptavidin beads in separate tubes by incubation at room temperature for 30 minutes in EK assay buffer (20 mM Tris-HCl, pH 7.4, 50 mM NaCl, 2 mM CaCl2, 0.05 % Triton X-100). After washing the bead bound phage were incubated with recombinant light chain EK assay buffer at room temperature. The amplified phage populations from round 5 were tested for EK cleavage by phage Enzyme Linked Immunosorbant Assay (ELISA). Round 5 phage populations were screened against phage from the unselected substrate library as a negative control. Individual phage samples were allowed to bind streptavidin-coated microtiter wells and then subjected to different concentrations of EK for 2 hours at room temperature. Unreleased phage were detected using an anti-phage antibody-horseradish peroxidase (HRP) conjugate and HRP active assay. The decline in absorbance at 630 nm in streptavidin-bound phage with increasing EK concentrations observed for the round 5 phage populations indicated successful selection for EK substrates.

L112 ANSWER 5 OF 9 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

AN 2001-308618 [32] WPIX

DNC C2001-095392

TI New fusion protein containing nucleotide-binding and ligand-binding domains, useful e.g. in gene therapy of cancer, provides ligand-activated control of gene expression.

DC B04 D16

IN BARBAS, C F; BEERLI, R; KADAN, M; KADAN, M J

PA (NOVS) NOVARTIS AG; (SCRI) SCRIPPS RES INST; (BARB-I) BARBAS C F; (BEER-I) BEERLI R; (KADA-I) KADAN M J

CYC 95

PI WO 2001030843 A1 20010503 (200132)* EN 217 C07K014-47
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001011438 A 20010508 (200149) C07K014-47
EP 1226168 A1 20020731 (200257) EN C07K014-47
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
JP 2003512827 W 20030408 (200333) 226 C12N015-09
US 2003186841 A1 20031002 (200365) A61K031-00

NZ 518218 A 20040430 (200431) C07K014-47
ADT WO 2001030843 A1 WO 2000-EP10430 20001023; AU 2001011438 A AU 2001-11438 20001023; EP 1226168 A1 EP 2000-972849 20001023, WO 2000-EP10430 20001023; JP 2003512827 W WO 2000-EP10430 20001023, JP 2001-533840 20001023; US 2003186841 A1 CIP of US 1999-433042 19991025, Cont of US 2000-586625 20000602, US 2003-422934 20030423; NZ 518218 A NZ 2000-518218 20001023, WO 2000-EP10430 20001023
FDT AU 2001011438 A Based on WO 2001030843; EP 1226168 A1 Based on WO 2001030843; JP 2003512827 W Based on WO 2001030843; NZ 518218 A Based on WO 2001030843
PRAI US 2000-586625 20000602; US 1999-433042 19991025;
US 2003-422934 20030423
IC ICM A61K031-00; C07K014-47; C12N015-09
ICS A61K009-127; A61K035-76; A61K038-00; A61K038-17; A61K048-00; A61P035-00; A61P043-00; C07H021-04; C07K014-705; C07K014-72; **C07K019-00**; C12N001-15; C12N001-19; C12N005-06; C12N005-10; C12N015-62; C12N015-86; **C12P021-02**
AB WO 200130843 A UPAB: 20010611
NOVELTY - Fusion protein (I) comprising a nucleotide-binding domain (NBD) linked to a ligand-binding domain (LBD) of an **intracellular** receptor (ICR). NBD is a polydactyl zinc finger protein, or a modular part of it, that interacts specifically with a contiguous sequence of at least 3 nucleotides (nt), and (I) functions as a ligand-activated transcriptional regulator.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included fort he following:

(a) nucleic acid (II) that encodes (I);

(b) vector containing (II);

(c) cell containing the vector of (b);

(d) combination of (I) or (II) with a regulatable expression cassette containing at lest one response element **recognized** by NBD;

(e) composition for regulating gene expression comprising (I) or (II) plus an excipient;

(f) regulating gene expression in a cell by introducing (I) or (II) then treating the cell with a ligand that interacts with LBD; and

(g) non-viral delivery system comprising (I) or (II).

ACTIVITY - Anticancer; Antiproliferative.

MECHANISM OF ACTION - Ligand-activated regulation of transcription.

USE - (I), or the nucleic acid (II) that encodes it, is used to regulate gene expression, particularly in gene therapy, especially of malignant or non-malignant proliferative disease (cancer, psoriasis, Behcet syndrome etc.), e.g. where induced by viruses in humans or plants, also genetic and/or acquired diseases.

ADVANTAGE - (I) can be designed to **target** any selected gene (endogenous or exogenous), and can be made to have different selectivity or specificity for endogenous or exogenous ligands.

Dwg.0/27
FS CPI
FA AB; DCN
MC CPI: B04-E03; B04-E08; B04-F0100E; B04-F1100E; B04-J01; B04-K01; B04-L01; B04-N04; B14-H01; B14-N17C; D05-H12C; D05-H12E; D05-H14; D05-H18
TECH UPTX: 20010611
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Protein: (I) also includes a transcription regulating domain (TRD), either an activating domain, e.g. from VP16, STAT-6 or a nuclear hormone receptor, or a repressor domain, e.g. ERD, KRAB, SID, deacetylase or their derivatives, multimers or combinations. ICR is particularly a steroid receptor, e.g. a nuclear hormone (e.g. progesterone) receptor and LBD has altered ligand specificity compared with the native receptor, especially so that it is not significantly activated by endogenous ligands. The zinc-finger peptide (i) binds to (GNN)n

N = any nucleotide;

n = 1-6, preferably 3-6

; (ii) comprises modular units from a C2H2 peptide, or its variants, that **target** (I) to an exogenous or endogenous gene containing a specific nucleotide sequence, or (iii) has at least one, preferably 3, zinc fingers, or variants, that bind to a **target** nucleic acid, particularly with dissociation constant less than 1 nM.
Preferred Nucleic Acid: (II) is any of 18 sequences reproduced, containing 1404-7038 base pair. Preferred Vectors: These are particularly viral, derived from adeno, adeno-associated, herpes, vaccinia or lenti viruses.
Preferred Cassette: In the combination of (d), the cassette includes a gene that expresses a therapeutic protein and has 3-6 response elements. It may be present in the same component as (I)/(II), or in a separate one. Typical therapeutic proteins are growth factors, tumor necrosis factor (or its receptor), enzymes, hormones etc.
Preferred Method: In (f), the **target** nucleic acid is endogenous to the cell or is introduced in a cassette (at the same time as (I)/(II), or a different time). The ligand is applied after introduction of (I)/(II) and cells are particularly mammalian.
Preferred System: The system of (g), which may also include an expression cassette containing a nucleotide sequence with which NBD interacts, is e.g. a ligand-DNA complex; direct injection of DNA; calcium phosphate precipitation, a gene gun; electroporation; a liposome or lipofection.

ABEX UPTX: 20010611
ADMINISTRATION - (I), or nucleic acid encoding it, and the activating ligand, are administered by injection, orally etc., or cells are modified ex vivo then returned to the patient. Typical unit doses are 103-1015, particularly 106-1012, viral particles.

EXAMPLE - The fusion protein C7BDA comprises (i) the DNA-binding domain of the Zif268-C7 zinc finger and (ii) a truncated ligand-binding domain of the human estrogen receptor. The nucleic acid encoding it was assembled conventionally and tested by expression in HeLa or COS cells for regulating the expression of the reporter construct 6x2C7pGL3, containing six copies of the C7 binding site, upstream of the SV40 promoter, controlling the luciferase gene. About 24 hr after transfection, the cells were treated with 100 nM of 17beta-estradiol or 4-hydroxytamoxifen (ligands) and after a further 24 hr, assayed for luciferase expression. The fusion protein had an estrogen-dependent effect on luciferase expression, with a 2- to 9-fold induction.

L112 ANSWER 6 OF 9 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 1998-388122 [33] WPIX
DNC C1998-117528
TI Nucleic acid encoding fusion protein containing mistletoe lectin A chain - useful for treatment of proliferative and autoimmune diseases, allergies and tumours.
DC B04 D16
IN ECK, J; SCHMIDT, A; ZINKE, H
PA (BRAI-N) BRAIN BIOTECHNOLOGY RES & INFORMATION NE; (VISC-N) VISCUM AG; (ECKJ-I) ECK J; (SCHM-I) SCHMIDT A; (ZINK-I) ZINKE H
CYC 79
PI WO 9829540 A2 19980709 (199833)* GE 115 C12N015-00
RW: AT BE CH DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN
AU 9860924 A 19980731 (199849) C12N015-00
EP 1012256 A2 20000628 (200035) GE C12N015-00
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
DE 19880004 T 20000615 (200036) C12N015-62
US 2002045208 A1 20020418 (200228) C12N015-74
EP 1012256 B1 20040331 (200426) GE C12N015-62
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

DE 59811111 G 20040506 (200434) C12N015-62
ADT WO 9829540 A2 WO 1998-EP9 19980102; AU 9860924 A AU 1998-60924 19980102; EP 1012256 A2 EP 1998-905267 19980102, WO 1998-EP9 19980102; DE 19880004 T DE 1998-1080004 19980102, WO 1998-EP9 19980102; US 2002045208 A1 Cont of WO 1998-EP9 19980102, US 1999-347064 19990702; EP 1012256 B1 EP 1998-905267 19980102, WO 1998-EP9 19980102; DE 59811111 G DE 1998-511111 19980102, EP 1998-905267 19980102, WO 1998-EP9 19980102
FDT AU 9860924 A Based on WO 9829540; EP 1012256 A2 Based on WO 9829540; DE 19880004 T Based on WO 9829540; EP 1012256 B1 Based on WO 9829540; DE 59811111 G Based on EP 1012256, Based on WO 9829540
PRAI EP 1997-100012 19970102
IC ICM C12N015-00; C12N015-62; C12N015-74
ICS A61K035-78; A61K038-16; A61K047-48; C07H021-04; **C07K019-00**; C12N001-00; C12N001-15; C12N001-20; C12N001-21; C12N015-09; C12N015-29; C12N015-63; C12N015-70; **C12P021-02**; **C12P021-06**; C12Q001-02; C12Q001-68
AB WO 9829540 A UPAB: 19980819

Nucleic acid (I) encodes a fusion protein (II) which comprises:

(a) an effector module (E) that is cytotoxic **intracellularly**
;

(b) a processing module (P), covalently bonded to (E) and containing a protease **recognition** sequence, and

(c) a **targeting** module (T), covalently bonded to (P), able to bind specifically to the surface of a cell so as to mediate internalisation of (II).

(E) is mistletoe lectin (ML) A-chain, its fragments or derivatives and/or (P) is the ML-propeptide, or its fragments or derivatives, cleavable by protease.

Also claimed are:

(1) vectors containing (I);

(2) hosts transformed with (1) or with (I);

(3) the fusion protein (II);

(4) a composition (A) containing:

(a) (I), (II) or (1), and

(b) a modulator module (M), covalently bonded to (P) and/or (E) and able to modulate the **intracellular** toxicity of (E), or a vector containing nucleic acid that encodes (M);

(5) a method for the in vitro identification of M, and

(6) the use of ML B-chain, or its fragments or derivatives, for modulating **intracellular** activity of toxins (Tox).

USE - The hosts of (2) are used to produce (II) which is useful for treating disorders involving proliferation and/or elevated activation of cells, especially autoimmune disease, allergy and tumours.

(II) are administered e.g. by injection or topically but especially by intravenous injection, at 1 ng to 500 mu g/kg/day, or for ex vivo use at 1 pg to 500 ng/ml. Where (II) is delivered in the form of nucleic acid vectors, the dose is 106-1022 gene copies.

ADVANTAGE - (II) can develop toxic activity in a wide range of **target** cells. P prevents extracellular dissociation, and (II) based on ML A-chain are far more active than those based on ricin and do have the associated problems of non-specific toxicity. (II) may be expressed in Escherichia coli in a non-glycosylated form that does not bind to sugar receptors in the liver, and which has a long half-life in the blood. (II) has lower molecular weight than most immunotoxins and so is less likely to induce an immune response while being better able to penetrate through dense tissue. Where ML B-chain is used, it actively assists in translocation of the ML A-chain from the endoplasmic reticulum to the cytoplasm.

Dwg.0/29

FS CPI
FA AB
MC CPI: B04-E03F; B04-E08; B04-N04; B11-C08E; B12-K04A; B14-G02A; B14-G02D; B14-H01; D05-H12B2; D05-H12E; D05-H14B2; D05-H16A; D05-H17C

```
L112 ANSWER 7 OF 9  WPIX  COPYRIGHT 2004 THE THOMSON CORP on STN
AN   1995-292893 [38]   WPIX
CR   1992-331474 [40]; 1995-067330 [09]; 1996-129034 [13]; 1996-402134 [40];
     1996-402358 [40]; 1999-044582 [04]
DNC  C1995-131866
TI   Target cytolysis of HIV-infected cells - by chimeric CD4
     receptor-bearing cells.
DC   B04 D16
IN   BANAPOUR, B; KOLANUS, W; ROMEO, C; SEED, B
PA   (GEHO) GEN HOSPITAL CORP; (BANA-I) BANAPOUR B; (KOLA-I) KOLANUS W;
     (ROME-I) ROMEO C; (SEED-I) SEED B
CYC  36
PI   WO 9521528      A1 19950817 (199538)* EN  118   A01N063-00
        RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
         W: AU BR BY CA CN CZ FI HU JP KR MX NO NZ PL RU SI UA
     AU 9515653      A  19950829 (199548)
     ZA 9500921      A  19960327 (199619)      117   C12N000-00
     NO 9603379      A  19961011 (199650)            C12N005-00
     FI 9603150      A  19961010 (199702)            C12N000-00
     EP 750457       A1 19970102 (199706)  EN
         R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
     CZ 9602331      A3 19970716 (199735)            A61K039-00
     BR 9506783      A  19971014 (199747)
     HU 75375        T  19970528 (199803)
     JP 09512421     W  19971216 (199809)      115   C12N015-09
     KR 97701004     A  19970317 (199813)            A01N063-00
     NZ 279123       A  19980325 (199818)            C12N005-10
     BR 1100759      A3 19980519 (199826)            C07K014-73
     AU 690204       B  19980423 (199828)
     AU 9877442      A  19981022 (199903)
     US 5851828      A  19981222 (199907)            C12N005-10
     MX 9603384      A1 19971201 (199936)            A01N063-00
     AU 724652       B  20000928 (200052)            A01N063-00
     CN 1146136      A  19970326 (200106)            A01N063-00
     CN 1158552      A  19970903 (200140)            A01N063-00
     US 6284240      B1 20010904 (200154)            A61K048-00
     RU 2173167      C2 20010910 (200168)            A61K038-00
     HU 220100       B  20011029 (200175)            A01N063-00
     KR 289253       B  20011130 (200246)            A01N063-00
     MX 205280       B  20011123 (200282)            A01N063-00
     EP 781095       B1 20030312 (200319)  EN        A01N063-00
         R: AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE SI
     US 2003138410   A1 20030724 (200352)#           A61K048-00
     ES 2191058      T3 20030901 (200365)            A01N063-00
     CZ 293943       B6 20040818 (200457)            A01N063-00
     CZ 293969       B6 20040915 (200462)            C12N005-00
ADT  WO 9521528 A1 WO 1995-US454 19950112; AU 9515653 A AU 1995-15653 19950112;
     ZA 9500921 A ZA 1995-921 19950206; NO 9603379 A WO 1995-US454 19950112, NO
     1996-3379 19960813; FI 9603150 A WO 1995-US454 19950112, FI 1996-3150
     19960812; EP 750457 A1 EP 1995-907414 19950112, WO 1995-US454 19950112; CZ
     9602331 A3 WO 1995-US454 19950112, CZ 1996-2331 19950112; BR 9506783 A BR
     1995-6783 19950112, WO 1995-US454 19950112; HU 75375 T WO 1995-US454
     19950112, HU 1996-2182 19950112; JP 09512421 W JP 1995-521213 19950112, WO
     1995-US454 19950112; KR 97701004 A WO 1995-US454 19950112, KR 1996-704450
     19960814; NZ 279123 A NZ 1995-279123 19950112, WO 1995-US454 19950112; BR
     1100759 A3 BR 1997-1100759 19970512; AU 690204 B AU 1995-15653 19950112;
     AU 9877442 A Div ex AU 1995-15653 19950112, AU 1998-77442 19980722; US
     5851828 A CIP of US 1991-665961 19910307, CIP of US 1992-847566 19920306,
     CIP of US 1994-195395 19940214, US 1994-284391 19940802; MX 9603384 A1 MX
     1996-3384 19960814; AU 724652 B Div ex AU 1995-15653 19950112, AU
     1998-77442 19980722; CN 1146136 A CN 1995-192559 19950112; CN 1158552 A CN
     1995-195183 19950726; US 6284240 B1 CIP of US 1991-665961 19910307, CIP of
```

US 1992-847566 19920306, CIP of US 1994-195395 19940214, Div ex US 1994-284391 19940802, US 1998-218950 19981222; RU 2173167 C2 WO 1995-US454 19950112, RU 1996-118239 19950112; HU 220100 B WO 1995-US454 19950112, HU 1996-2182 19950112; KR 289253 B WO 1995-US454 19950112, KR 1996-704450 19960814; MX 205280 B MX 1996-3384 19960814; EP 781095 B1 EP 1995-928152 19950726, WO 1995-US9468 19950726; US 2003138410 A1 CIP of US 1991-665961 19910307, CIP of US 1992-847566 19920306, CIP of US 1994-195395 19940214, Cont of US 1998-218950 19981222, US 2001-939537 20010824; ES 2191058 T3 EP 1995-928152 19950726; CZ 293943 B6 WO 1995-US9468 19950726, CZ 1997-264 19950726; CZ 293969 B6 WO 1995-US454 19950112, CZ 1996-2331 19950112

FDT AU 9515653 A Based on WO 9521528; EP 750457 A1 Based on WO 9521528; CZ 9602331 A3 Based on WO 9521528; BR 9506783 A Based on WO 9521528; HU 75375 T Based on WO 9521528; JP 09512421 W Based on WO 9521528; KR 97701004 A Based on WO 9521528; NZ 279123 A Based on WO 9521528; AU 690204 B Previous Publ. AU 9515653, Based on WO 9521528; AU 724652 B Div ex AU 690204, Previous Publ. AU 9877442; US 6284240 B1 Div ex US 5851828; RU 2173167 C2 Based on WO 9521528; HU 220100 B Previous Publ. HU 75375, Based on WO 9521528; KR 289253 B Previous Publ. KR 97701004, Based on WO 9521528; EP 781095 B1 Based on WO 9603883; ES 2191058 T3 Based on EP 781095; CZ 293943 B6 Previous Publ. CZ 9700264, Based on WO 9603883; CZ 293969 B6 Previous Publ. CZ 9602331, Based on WO 9521528

PRAI US 1994-284391 19940802; US 1994-195395 19940214;
US 1991-665961 19910307; US 1992-847566 19920306;
US 1995-394388 19950224; US 1998-218950 19981222;
US 2001-939537 20010824

REP 05Jnl.Ref; EP 394827; WO 9210591; WO 9215322; 06Jnl.Ref; JP 1063394

IC ICM A01N063-00; A61K038-00; A61K039-00; A61K048-00; C07K014-73; C12N000-00; C12N005-00; C12N005-10; C12N015-09
ICS A61K035-12; A61K035-14; A61K035-26; A61K038-17; A61K039-21; A61P031-18; C07H017-00; C07H021-04; C07K014-725; **C07K019-00** ; C12N005-06; C12N005-12; C12N005-16; C12N015-00; C12N015-11; C12N015-12; C12N015-62; C12N015-63; C12N015-85; **C12P021-06**; C12Q001-70

AB WO 9521528 A UPAB: 20040928
Directing a cellular immune response against an HIV-infected cell in a mammal comprising administering to the mammal an amount of therapeutic cells which express a membrane bound, proteinaceous chimeric receptor comprising: (a) an extracellular portion which includes a fragment of CD4 which is capable of specifically **recognising** and binding the HIV-infected cell but which does not mediate HIV infection; and (b) an **intracellular** portion which is capable of signalling the therapeutic cell to destroy the receptor-bound HIV-infected cell. Also claimed are: (A) a cell, as above, which expresses a proteinaceous membrane-bound chimeric receptor; (B) a DNA encoding a chimeric receptor as in (A); and (C) a vector comprising the chimeric receptor DNA of (B).
USE - The method concerns functional chimeras between CD4 fragments and immune cell receptors which are capable of directing immune cells to lyse HIV-infected cells, but which do not render the immune cells susceptible to HIV infection. The transformed cells are used for immunodeficiency virus therapy.
Dwg.0/27

FS CPI
FA AB
MC CPI: B04-E01; B04-E08; B04-F01; B04-F11; B14-G03; D05-H12B2; D05-H12E; D05-H14; D05-H17B4

L112 ANSWER 8 OF 9 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 1995-067330 [09] WPIX
CR 1992-331474 [40]; 1995-292893 [38]; 1996-129034 [13]; 1996-402134 [40]; 1996-402358 [40]; 1999-044582 [04]
DNC C1995-029805
TI Chimeric receptors on therapeutic cells,eg. cytotoxic T-lymphocytes - also DNA and vectors encoding the receptors, useful for specific

recognition and destruction of **target** cells..

DC B04 D16

IN KOLANUS, W; ROMEO, C; SEED, B

PA (GEHO) GEN HOSPITAL CORP; (KOLA-I) KOLANUS W; (ROME-I) ROMEO C; (SEED-I) SEED B

CYC 29

PI	WO 9502686	A1	19950126	(199509)*	EN	78	C12N005-10	
	RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE							
	W: AU CA CZ FI HU JP KR NO NZ RU							
	AU 9473140	A	19950213	(199519)				
	ZA 9405204	A	19950726	(199535)		85	C12N000-00	
	FI 9600178	A	19960115	(199613)			C12N000-00	
	NO 9600175	A	19960315	(199619)			C12N005-10	
	CZ 9503408	A3	19960814	(199639)			C12N015-10	
	JP 09500020	W	19970107	(199711)		80	C12N005-10	
	HU 74252	T	19961128	(199712)				
	EP 804552	A1	19971105	(199749)	EN			
	R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE							
	NZ 269312	A	19980226	(199813)			C12N005-10	
	AU 686646	B	19980212	(199814)				
	AU 9864767	A	19980702	(199837)			C07K019-00	<--
	AU 712245	B	19991104	(200003)			A61K045-05	
	US 6004811	A	19991221	(200006)			C12N005-00	
	RU 2158305	C2	20001027	(200106)			C12N015-00	
	KR 278352	B	20010115	(200207)			C12N005-10	
	US 6392013	B1	20020521	(200239)			C12P021-02	<--
	US 2003053994	A1	20030320	(200323)			A61K048-00	
	EP 804552	B1	20030409	(200325)	EN		C12N005-10	
	R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE							
	CZ 291754	B6	20030514	(200337)			C12N005-10	
	DE 69432487	E	20030515	(200340)			C12N005-10	
	ES 2197166	T3	20040101	(200412)			C12N005-10	
	NO 316942	B1	20040705	(200444)			C12N005-10	
	JP 2004222735	A	20040812	(200453)		36	C12N015-09	

ADT WO 9502686 A1 WO 1994-US6675 19940614; AU 9473140 A AU 1994-73140 19940614; ZA 9405204 A ZA 1994-5204 19940715; FI 9600178 A WO 1994-US6675 19940614, FI 1996-178 19960115; NO 9600175 A WO 1994-US6675 19940614, NO 1996-175 19960115; CZ 9503408 A3 CZ 1995-3408 19940614; JP 09500020 W WO 1994-US6675 19940614, JP 1995-504542 19940614; HU 74252 T WO 1994-US6675 19940614, HU 1996-84 19940614; EP 804552 A1 EP 1994-923200 19940614, WO 1994-US6675 19940614; NZ 269312 A NZ 1994-269312 19940614, WO 1994-US6675 19940614; AU 686646 B AU 1994-73140 19940614; AU 9864767 A Div ex AU 1994-73140 19940614, AU 1998-64767 19980507; AU 712245 B Div ex AU 1994-73140 19940614, AU 1998-64767 19980507; US 6004811 A CIP of US 1991-665961 19910307, CIP of US 1992-847566 19920306, Cont of US 1993-93210 19930716, US 1995-394912 19950224; RU 2158305 C2 WO 1994-US6675 19940614, RU 1996-105032 19940614; KR 278352 B WO 1994-US6675 19940614, KR 1996-700185 19960115; US 6392013 B1 CIP of US 1991-665961 19910307, CIP of US 1992-847566 19920306, Cont of US 1993-93210 19930716, Div ex US 1995-394912 19950224, US 1997-889712 19970707; US 2003053994 A1 CIP of US 1991-665961 19910307, CIP of US 1992-847566 19920306, Cont of US 1993-93210 19930716, Div ex US 1995-394912 19950224, Div ex US 1997-889712 19970707, US 2002-151193 20020520; EP 804552 B1 EP 1994-923200 19940614, WO 1994-US6675 19940614; CZ 291754 B6 WO 1994-US6675 19940614, CZ 1995-3408 19940614; DE 69432487 E DE 1994-632487 19940614, EP 1994-923200 19940614, WO 1994-US6675 19940614; ES 2197166 T3 EP 1994-923200 19940614; NO 316942 B1 WO 1994-US6675 19940614, NO 1996-175 19960115; JP 2004222735 A Div ex JP 1995-504542 19940614, JP 2004-125883 20040421

FDT AU 9473140 A Based on WO 9502686; JP 09500020 W Based on WO 9502686; HU 74252 T Based on WO 9502686; EP 804552 A1 Based on WO 9502686; NZ 269312 A Based on WO 9502686; AU 686646 B Previous Publ. AU 9473140, Based on WO 9502686; AU 712245 B Div ex AU 686646, Previous Publ. AU 9864767; RU 2158305 C2 Based on WO 9502686; KR 278352 B Previous Publ. KR 96704025,

```
     Based on WO 9502686; US 6392013 B1 Div ex US 6004811; US 2003053994 A1 Div
     ex US 6004811, Div ex US 6392013; EP 804552 B1 Based on WO 9502686; CZ
     291754 B6 Previous Publ. CZ 9503408, Based on WO 9502686; DE 69432487 E
     Based on EP 804552, Based on WO 9502686; ES 2197166 T3 Based on EP 804552;
     NO 316942 B1 Previous Publ. NO 9600175
PRAI US 1993-93210         19930716; US 1991-665961       19910307;
     US 1992-847566        19920306; US 1995-394912       19950224;
     US 1997-889712        19970707; US 2002-151193       20020520
REP  5.Jnl.Ref; WO 9215322
IC   ICM  A61K045-05; A61K048-00; C07K019-00; C12N000-00; C12N005-00;
          C12N005-10; C12N015-00; C12N015-09; C12N015-10
     ICS  A61K035-14; A61K035-54; A61K038-48; A61K039-12; A61K047-42;
          A61P031-04; A61P031-10; A61P031-12; A61P031-18; A61P033-02;
          A61P037-04; A61P043-00; C07H021-00; C07K014-705; C07K016-46;
          C12N009-12; C12N015-11; C12N015-62; C12N015-63; C12P021-04;
          G01N000-00
ICA  C12P021-02
AB   WO    9502686 A UPAB: 20040818
     Cell expressing a membrane-bound, proteinaceous chimeric receptor
     comprises: (a) an intracellular portion of a protein-tyrosine
     kinase (I) which signals the therapeutic cell to destroy a receptor-bound
     target cell or target infective agent, and (b) an
     extracellular portion capable of specifically recognising and
     binding the target cell or infective agent. Also claimed is: (1)
     DNA encoding the chimeric receptor; and (2) a vector comprising this DNA.
          USE - The chimeric receptor allows the specific recognition
     and destruction of target cells, e.g. pathogens,
     pathogen-infected cells, tumour cells or autoimmune cells. It can also be
     used to control cell populations in vivo subsequent to genetic
     engineering, e.g. the use of tumour-infiltrating lymphocytes or natural
     killer cells to carry cytotoxic principles to tumour sites.
     Dwg.0/10
FS   CPI
FA   AB
MC   CPI: B04-E01; B04-E08; B04-F04; D05-H09; D05-H12C; D05-H12E; D05-H14B2;
          D05-H17C1

L112 ANSWER 9 OF 9  WPIX  COPYRIGHT 2004 THE THOMSON CORP on STN
AN   1992-331474 [40]    WPIX
CR   1995-067330 [09]; 1995-292893 [38]; 1996-129034 [13]; 1996-402134 [40];
     1996-402358 [40]; 1999-044582 [04]
DNC  C1992-147353
TI   Therapeutic cells expressing chimeric receptors - directing cellular
     response to an infective agent, useful in treating HIV-1, AIDS
     Pneumocystis carinii infections etc..
DC   B04 D16
IN   KOLANUS, W; ROMEO, C; SEED, B
PA   (GEHO) GEN HOSPITAL CORP; (GEHO) GEN HOSPITAL CORP OFFICE TECHNOLOGY
CYC  32
PI   WO 9215322       A1 19920917 (199240)* EN  114    A61K037-12
        RW: AT BE CH DE DK ES FR GB GR IT LU MC NL SE
         W: AU BR CA CS FI HU JP KR NO PL RU
     AU 9215559       A  19921006 (199301)
     ZA 9201650       A  19921230 (199306)      111    A61K000-00
     FI 9303882       A  19930906 (199347)             C12N000-00
     EP 574512        A1 19931222 (199351)  EN
         R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE
     NO 9303169       A  19931104 (199405)             C12N005-00
     NZ 241855        A  19940427 (199420)             A61K035-12
     PT 100207        A  19940531 (199421)             G01N033-00
     CZ 9301840       A3 19940413 (199422)
     HU 65631         T  19940728 (199431)
     BR 9205736       A  19940927 (199440)
```

```
     SK 9300956      A3 19940907 (199440)
     JP 06509462     W  19941027 (199502)          C12N005-10
     AU 662136       B  19950824 (199542)          C07K015-12
     AU 9530328      A  19960111 (199609)          C12N015-12
     CZ 281881       B6 19970312 (199717)          C07K017-00
     EP 574512       A4 19970312 (199729)
     AU 689289       B  19980326 (199826)          C12N015-12
     HU 218732       B  20001128 (200103)          C12N005-10
     RU 2161044      C2 20001227 (200112)          A61K048-00
     KR 257780       B1 20000701 (200131)          A61K038-00
     EP 574512       B1 20030205 (200318)  EN      A61K038-16
         R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE
     DE 69232921     E  20030313 (200326)          A61K038-16
     ES 2191006      T3 20030901 (200365)          A61K038-16
     SK 283643       B6 20031104 (200377)          C07K017-02
     IL 101147       A  20040620 (200446)          C12N015-12
     NO 317202       B1 20040920 (200462)          C12N015-62
```

ADT WO 9215322 A1 WO 1992-US1785 19920306; AU 9215559 A AU 1992-15559 19920306, WO 1992-US1785 19920306; ZA 9201650 A ZA 1992-1650 19920305; FI 9303882 A WO 1992-US1785 19920306, FI 1993-3882 19930906; EP 574512 A1 EP 1992-907958 19920306, WO 1992-US1785 19920306; NO 9303169 A WO 1992-US1785 19920306, NO 1993-3169 19930906; NZ 241855 A NZ 1992-241855 19920305; PT 100207 A PT 1992-100207 19920306; CZ 9301840 A3 CZ 1993-1840 19920306; HU 65631 T WO 1992-US1785 19920306, HU 1993-2524 19920306; BR 9205736 A BR 1992-5736 19920306, WO 1992-US1785 19920306; SK 9300956 A3 SK 1993-956 19930907, WO 1992-US1785 ; JP 06509462 W JP 1992-507575 19920306, WO 1992-US1785 19920306; AU 662136 B AU 1992-15559 19920306; AU 9530328 A Div ex AU 1992-15559 19920306, AU 1995-30328 19950830; CZ 281881 B6 WO 1992-US1785 19920306, CZ 1993-1840 19920306; EP 574512 A4 EP 1992-907958 ; AU 689289 B Div ex AU 1992-15559 19920306, AU 1995-30328 19950830; HU 218732 B WO 1992-US1785 19920306, HU 1993-2524 19920306; RU 2161044 C2 WO 1992-US1785 19920306, RU 1993-55035 19920306; KR 257780 B1 WO 1992-US1785 19920306, KR 1993-702656 19930906; EP 574512 B1 EP 1992-907958 19920306, WO 1992-US1785 19920306; DE 69232921 E DE 1992-632921 19920306, EP 1992-907958 19920306, WO 1992-US1785 19920306; ES 2191006 T3 EP 1992-907958 19920306; SK 283643 B6 WO 1992-US1785 19920306, SK 1993-956 19920306; IL 101147 A IL 1992-101147 19920305; NO 317202 B1 WO 1992-US1785 19920306, NO 1993-3169 19930906

FDT AU 9215559 A Based on WO 9215322; EP 574512 A1 Based on WO 9215322; HU 65631 T Based on WO 9215322; BR 9205736 A Based on WO 9215322; JP 06509462 W Based on WO 9215322; AU 662136 B Previous Publ. AU 9215559, Based on WO 9215322; CZ 281881 B6 Previous Publ. CZ 9301840, Based on WO 9215322; AU 689289 B Previous Publ. AU 9530328; HU 218732 B Previous Publ. HU 65631, Based on WO 9215322; RU 2161044 C2 Based on WO 9215322; EP 574512 B1 Based on WO 9215322; DE 69232921 E Based on EP 574512, Based on WO 9215322; ES 2191006 T3 Based on EP 574512; SK 283643 B6 Previous Publ. SK 9300956, Based on WO 9215322; NO 317202 B1 Previous Publ. NO 9303169

PRAI US 1991-665961 19910307

REP 11Jnl.Ref; 1.Jnl.Ref; WO 9210591

IC ICM A61K000-00; A61K035-12; A61K037-12; A61K038-00; A61K038-16; A61K048-00; C07K015-12; C07K017-00; C07K017-02; C12N000-00; C12N005-00; C12N005-10; C12N015-12; C12N015-62; G01N033-00
ICS A61K039-395; A61K039-42; A61P035-00; C07H021-00; C07K003-00; C07K013-00; C07K014-00; C07K014-704; C07K014-705; C07K014-725; C07K014-73; C07K014-735; C07K015-00; C07K015-06; C07K015-28; **C07K019-00**; C12N005-06; C12N005-16; C12N015-00; C12N015-09; C12N015-63; C12N015-79; C12N015-85; **C12P021-08**

AB WO 9215322 A UPAB: 20040928
Directing a cellular response to an infective agent, to a cell infected with the agent, to a tumour or cancerous cell or to an autoimmune-generated cell in a mammal, comprises administering to the mammal an effective amount of therapeutic cells which are capable of specifically **recognising** and destroying the agent or cell.

Also claimed are: (1) a cell which expresses a proteinaceous membrane-bound chimeric receptor which comprises (a) an extracellular portion which is capable of specifically **recognising** and binding an effective agent, a cell infected with an infective agent, a tumour or a cancerous cell, or an autoimmune-generated cell and (b) an **intracellular** portion or transmembrane portion derived from a T-cell receptor, an Fc receptor, or a B cell receptor which is capable of signalling the cell to destroy a receptor-bound agent or receptor-bound cell; (2) DNA encoding the chimeric receptor of (1); (3) a vector comprising the DNA of (2); and (4) an antibody which specifically **recognises** and binds the chimeric receptor of (1).

USE/ADVANTAGE - The method allows the **target recognition** potential of an immune system cell to be specifically redirected to the antigen **recognised** by the extracellular antibody portion. Thus immune system cells 'aimed' with the chimera would respond to the presence of the pathogen appropriate to their lineage or with tumour cells immune response could be beneficially elevated. The advantage of this method over the use of antibodies is that the native receptor for the pathogen may have a uniquely high selectivity or affinity for the pathogen, allowing a greater degree of precision in the resulting immune response. It may also be used in the control of cell populations in vivo subsequent to other forms of genetic engineering. Specifically it may be used to direct cellular response to an HIV infected
Dwg.0/19

```
FS   CPI
FA   AB
MC   CPI: B04-B04A1; B04-B04C6; B04-B04D1; B12-A01; B12-A06; B12-G07; D05-H06;
          D05-H07; D05-H12


=>

=> d l113 all abeq tech abex tot

L113 ANSWER 1 OF 16  WPIX  COPYRIGHT 2004 THE THOMSON CORP on STN
AN   2003-301008 [29]   WPIX
DNN  N2003-239424        DNC C2003-078601
TI   Use of collapsin response mediator protein for treating T lymphocyte
     dysfunction, e.g. viral infection or leukemia, also for drug screening,
     diagnosis and prognosis.
DC   B04 D16 S03
IN   ANTOINE, J C; BELIN, M F; COLAS, P; GIRAUDON, P; HONNORAT, J;
     MALCUS, C; ANTOINE, J; BELIN, M
PA   (INRM) INSERM INST NAT SANTE & RECH MEDICALE
CYC  102
PI   WO 2003022298    A2 20030320 (200329)* FR   58    A61K038-17
        RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU
            MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
         W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
            DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
            KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
            RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA
            ZM ZW
     FR 2830762       A1 20030418 (200329)             A61K038-17
     FR 2829392       A1 20030314 (200330)             A61K038-17
     EP 1435993       A2 20040714 (200446)  FR         A61K038-17
         R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC
            MK NL PT RO SE SI SK TR
     AU 2002341090    A1 20030324 (200460)             A61K038-17
ADT  WO 2003022298 A2 WO 2002-FR3056 20020909; FR 2830762 A1 FR 2001-13342
     20011016; FR 2829392 A1 FR 2001-11627 20010907; EP 1435993 A2 EP
     2002-774915 20020909, WO 2002-FR3056 20020909; AU 2002341090 A1 AU
     2002-341090 20020909
```

FDT EP 1435993 A2 Based on WO 2003022298; AU 2002341090 A1 Based on WO 2003022298
PRAI FR 2001-13342 20011016; FR 2001-11627 20010907
IC ICM A61K038-17
ICS A61K031-7088; A61K039-395; A61K048-00; A61P025-00; A61P029-00; A61P035-02; A61P037-00; **C07K014-47**; C12Q001-68; G01N033-50; G01N033-68
AB WO2003022298 A UPAB: 20030505
NOVELTY - Use (M1) of:
(i) CRMP (collapsin response mediator protein) (I), or its active fragments;
(ii) nucleic acid (II) encoding (i);
(iii) antisense nucleic acid that hybridizes to (II); or
(iv) anti-CRMP antibodies for treating diseases involving dysfunction of T lymphocytes, i.e. T cell leukemia or lymphoma; viral infections; prion diseases and demyelinizing neuroinflammatory diseases such as multiple sclerosis, is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
in vitro screening (M2) for molecules useful for treating prion diseases, using CRMP; and
in vitro prognostic and/or diagnostic method (M3) for diseases associated with immune system dysfunction based on detecting expression or localization of CRMP.
ACTIVITY - Cytostatic; Virucide; Anti-HIV; Neuroprotective; Immunomodulator.
No details of tests for these activities are given.
MECHANISM OF ACTION - Modulating expression or activity of CRMP which are involved in signaling pathways leading to proliferation, death (apoptosis), maturation and 'education' of lymphocytes. Blocking of CRMP also blocks the effect of pathological prion proteins. CRMP is overexpressed in T cells of patients with immune system disorders.
USE - (I) and related materials are used for treating diseases involving dysfunction of T lymphocytes, i.e. T cell leukemia or lymphoma; viral infections; prion diseases and demyelinizing neuroinflammatory diseases such as multiple sclerosis, specifically infection by herpes, measles, Epstein-Barr, human T-cell lymphotropic or human immune deficiency viruses. Also (i) CRMP is used to identify agents potentially useful for treating prion diseases and (ii) to detect abnormal expression or localization of CRMP in immune system cells, for diagnosis and prognosis of diseases of the immune system, e.g. the conditions specified above and autoimmune diseases.
Dwg.0/10
FS CPI EPI
FA AB; DCN
MC CPI: B04-C01; B04-E03F; B04-E05; B04-E06; B04-N02; B11-C07A; B11-C08E3; B11-C08E5; B12-K04A; B12-K04E; B12-K04F; B14-A02; B14-H01A; B14-S01; D05-A02B; D05-C11; D05-H09; D05-H11; D05-H12A; D05-H12D1; D05-H12D2; D05-H18B
EPI: S03-E14H
TECH UPTX: 20030505
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Materials: (I) is CRMP5.
TECHNOLOGY FOCUS - BIOLOGY - Preferred Process: In M1 a test compound is incubated with prion protein (PrP) and CRMP, and any compound that inhibits interaction between PrP and CRMP, or its dimer, is selected. In M3 immune system cells (especially lymphocytes, dendritic cells or monocytes) from a patient are examined for abnormal expression or localization of CRMP, relative to a control. CRMP expression is determined by amplification of mRNA (the specification includes sequences for reverse transcription PCR and probes for Southern blotting for all 5 isoforms of CRMP) or by immunoassay.
Preparation: Ab are prepared by usual methods of immunization and cell fusion, and may be used as fragments, in labeled form or as immunoconjugates.

```
ABEX              UPTX: 20030505
     WIDER DISCLOSURE - Disclosed is use of any CRMP modulator and use of
     anti-CRMP antibodies as diagnostic reagents.

     ADMINISTRATION - CRMP and the other therapeutic agents are preferably
     administered orally or by injection, at doses of 0.1 mug to 1 mg, protein
     or nucleic acid.

     EXAMPLE - Analysis of expression of mRNA for isoforms 1, 2 and 4 of
     collapsin response mediator protein, by reverse transcription PCR,
     indicated overexpression of all these isoforms in T cells of patients
     infected by HIV-1 or human T cell lymphotropic virus.

L113 ANSWER 2 OF 16  WPIX  COPYRIGHT 2004 THE THOMSON CORP on STN
AN   2001-565611 [63]   WPIX
DNN  N2001-421087        DNC C2001-167935
TI   Detecting chitinous material in a processed non-chitinous biological
     sample, involves contacting sample with lectin probe that binds chitin, in
     the presence of pectinase and detecting binding of lectin to chitin.
DC   B04 C06 C07 D13 D16 S03
IN   COHEN, B A; PAYNE, J J; POTTS, S J; SLAUGHTER, D C; THOMPSON, J
     F; KOHN, B A
PA   (REGC) UNIV CALIFORNIA; (COHE-I) COHEN B A; (PAYN-I) PAYNE J J; (POTT-I)
     POTTS S J; (SLAU-I) SLAUGHTER D C; (THOM-I) THOMPSON J F
CYC  96
PI   WO 2001067102    A2 20010913 (200163)* EN   49    G01N033-53
        RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
            NL OA PT SD SE SL SZ TR TZ UG ZW
         W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
            DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ
            LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD
            SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
     AU 2001041938    A  20010917 (200204)              G01N033-53
     US 2002107179    A1 20020808 (200254)              A61K038-16
     EP 1261872       A2 20021204 (200280)  EN          G01N033-53
         R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
            RO SE SI TR
     MX 2002008679    A1 20030201 (200413)              C12Q001-34
     US 6770453       B1 20040803 (200451)              C12Q001-34
ADT  WO 2001067102 A2 WO 2001-US6774 20010302; AU 2001041938 A AU 2001-41938
     20010302; US 2002107179 A1 CIP of US 2000-519533 20000306, US 2001-759815
     20010110; EP 1261872 A2 EP 2001-913259 20010302, WO 2001-US6774 20010302;
     MX 2002008679 A1 WO 2001-US6774 20010302, MX 2002-8679 20020905; US
     6770453 B1 US 2000-519533 20000306
FDT  AU 2001041938 A Based on WO 2001067102; EP 1261872 A2 Based on WO
     2001067102; MX 2002008679 A1 Based on WO 2001067102
PRAI US 2001-759815      20010110; US 2000-519533        20000306
IC   ICM  A61K038-16; C12Q001-34; G01N033-53
     ICS  C07K014-42; G01N021-64; G01N033-569
AB   WO 200167102 A UPAB: 20011031
     NOVELTY - Detecting chitinous material in processed non-chitinous
     biological sample (NCS) involves contacting NCS with lectin probe (I)
     which binds chitin (C), contacting NCS with a pectinase, and detecting
     binding of (I) to (C), NCS involves contacting NCS with fluorescently
     labeled (I) in solution at pH of 7-9 and detecting binding of (I) to (C),
     where binding in both cases indicates presence of (C) in NCS.
          DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the
     following:
          (1) a kit for detecting chitinous material in NCS comprises a first
     container containing chitinous material, and a second container containing
     pectinase;
          (2) detecting (M1) fluorochrome bound to one phase of a two-phase
     mixture involves contacting a transparent surface of a receptacle with a
```

solid or semi-solid phase of the two phase mixture, illuminating the solid or semi-solid phase of the two mixture through the transparent surface and detecting through the transparent surface a fluorochrome bound to the solid or semi-solid phase of the two-phase mixture;

(3) a surface-reading fluorometer comprising a receptacle having a transparent surface, the receptacle being compatible with centrifugation in a centrifuge, a light source for illuminating a sample through the transparent surface and a detector disposed to detect fluorescence through the transparent surface; and

(4) a biological sample (II) in which a lectin that specifically binds (C), is bound to a chitinous contaminant of the sample, where the lectin is labeled with a label that provides the signal distinguishable from a background signal, and indicates the presence or quantity of chitinous contaminant in the biological sample.

USE - Detecting chitinous material in processed and unprocessed biological sample such as an agricultural product such as a fruit e.g., tomato, pepper, grape, orange, apple, lemon or berry, vegetable, grain, forage, silage, juice, wood, flower or seed; wood product; a textile or an animal tissue product, by detecting binding of a lectin probe to (C) which comprises an insect, insect part, or any animal of the phylum Arthropoda, subphylum Crustacea. Alternately, the method involves detecting (C) which is a component of a microorganism such as fungus (of phylum Ascomycota, Basidomycota, Chytridiomycota, zygomycota or a member of phylum Oomycota in the Stramenopila kingdom), mold or yeast. Preferably, the method detects chitinous material of a fungus such as Cladosporium spp., Fusarium spp., Stemphylium spp., Alternaria spp., Geotrichum spp., Rhizopus spp., Botrytis spp., Phytophthora spp., or Pythium spp.. The chitinous material is detected in a processed biological sample which is a sample that has been subjected to comminuting, homogenizing, heating, evaporation, lyophylization, filtering, concentrating, filtering, fermenting, freezing or blanching (claimed). The methods are useful in commercial applications, particularly in food and agriculture industry.

ADVANTAGE - The methods are accurate, highly reproducible, and relatively inexpensive. The method show high reliability and high reproducibility and are well suited to mass screening. By using labeled lectins, the signal-to-noise ratio can be dramatically increased by contacting the sample with pectinase. The improvement in the signal-to-noise ratio results in an economical, commercially viable, reliable assay. The results can be obtained without multiple washing steps usually employed in an assay.

Dwg.0/8

FS CPI EPI
FA AB; DCN
MC CPI: B04-A08D; B04-C02E3; B04-L05C; B06-F03; B10-A07; B11-C07B3; B12-K04; C04-A08D; C04-C02E3; C04-L05C; C06-F03; C10-A07; C11-C07B3; C12-K04; D03-A04; D03-H02; D03-K04; D05-A02C; D05-H05; D05-H09
EPI: S03-E04D; S03-E14H4
TECH UPTX: 20011031

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: Detecting chitinous material in a processed NCS such as a fruit, vegetable, a fruit or vegetable juice that has been processed by comminuting, homogenizing, heating, evaporation, lyophylization, filtering, concentrating, filtering, fermenting, freezing or blanching involves contacting the sample with a lectin such as wheat germ agglutenin (WGA), succinylated WGA, pokeweed lectin, tomato lectin, potato lectin, barley lectin, rice lectin, stinging nettle lectin, a vicilin, a chitovibrin, Vibrio lectin, or a hevein; contacting the sample with polygalacturonase, pectinesterase, pectin lyase or hemicellulase and detecting binding of lectin to (C) by detecting a signal from fluorescent label labeling the lectin. The method is performed at a pH greater than 7.0 and preferably at a pH of 8.0. Detecting chitinous material in unprocessed NCS preferably involves contacting a NCS such as fruit, vegetable, or fruit or vegetable juice with a fluorescently labeled (I) and detecting binding of lectin as described above to (C), by

detecting a signal from the fluorescent label which labels the lectin. The method further involves contacting the biological sample with a pectinase as mentioned above. Detecting chitinous material in both processed and unprocessed NCS further involves contacting NCS with a blocking reagent such as serum albumin. Detecting lectin bound to (C) involves filtering the sample and eluting bound lectin. The eluting process involves contacting the lectin with (C), a (C) degradation product such as N-acetyl D-glucosamine or a (C) analogue. Lectin used in the processes is labeled with a detectable label such as radioactive label, magnetic label, colorimetric label, an enzymatic label, (preferably) a fluorescent label, metal, antibody, biotin, avidin or streptavidin and the detection process thus involves use of a fluorometer to detect the presence of the label. Most preferably the detection process involves filtering the sample, washing the filter to remove unbound (C), eluting bound lectin with a (C), a (C) degradation product or a (C) analogue, and detecting the eluted lectin with the fluorometer that uses a bandpass filter and is a surface reading fluorometer. In (M1), the receptacle is a centrifuge or a flow-through centrifuge. The contacting step involves spinning the receptacle so that the solid or semi-solid phase is deposited against the transparent surface. The two-phase mixture comprises a biological sample and the fluorochrome employed in the process is a (C)-specific fluorescently labeled lectin.
Preferred Kit: The first and the second containers of the kit are the same. The kit further comprises a label as described above for labeling the lectin, a transparent centrifugable receptacle for use with a surface reading flurometer and a bandpass filter for passing light emitted by a fluorescent label in the kit.
Preferred Sample: (II) is a processed sample with its pH ranging from 7-9 (basic) and is an agricultural product such as a fruit e.g., tomato, pepper, grape, orange, apple, lemon or berry, vegetable, grain, forage, silage, juice, wood, flower or seed. The sample further comprises an exogenously supplied pectinase.

ABEX UPTX: 20011031

EXAMPLE - Ripe, defect free processing tomatoes were washed and surface disinfected. Cultures of Alternaria alternata, Cladosporium herbarum, Fusarium oxysporum and Stemphylium botryosum, were grown to 21 days. Each fruit was pricked and inoculated with one of four fungal pathogens. The fruit were placed into an incubator and maintained until the fungi spoiled approximately 2 % by mass of the tomato tissue. The spoiled volume was cut from each fruit in a set and added to unspoiled tissue from additional ripe, defect free processing tomatoes to obtain 3.6 kg of juice containing 2% spoiled tissue (by mass). A separate set of 80 defect-free processing tomatoes were also comminuted for 40 seconds in the blender to obtain 3.6 kg of juice containing no spoiled tissue. The tomato juice with 2% spoiled tissue and the juice with no spoiled tissue were filtered and combined proportionally to obtain five juice samples with spoiled tissue dilution levels of 0.0%, 0.25%, 0.5%, 1.0% and 2.0% (by mass). Each dilution level was sub-divided into 40 ml replicate sub-samples, placed into sealable tubes, autoclaved and then stored at 8 degrees C for up to three weeks. Howard mold count (HMC) procedure was carried out for the five spoiled tissue dilution levels for each of the four fungal species. The HMC scores for the juice samples was 0-100% for all mold species except C.herbarum which had a maximum HMC of 96%. The average amount of mold for each species was 0.75% spoiled tissue by mass. The average HMC scores for each species however, ranged from a low of 37.4% for C.herbarum to a high of 64.2% for A.alternate. The HMC results were non-linear with spoiled tissue dilution level. Considerable variability, particularly at the intermediate spoiled tissue levels, was observed between the HMC scores obtained by the different quality control laboratories (QCL). The overall average coefficient of variation (CV) between the average HMC scores of all four quality control laboratories was 35%. Another set of 60 juice samples was used in the lectin assay. Ten ml of juice was centrifuged and supernatant were removed. Highly reactive non-specific binding sites were blocked and

50 microl of 1 mg/ml Fluoroscein isothiocyanate (FITC) labeled wheat germ agglutenin (WGA) lectin was added. The tube was shaken, lectin buffer (40 ml) was added, and centrifuged. The supernatant was removed, leaving the cells pelleted. The centrifuging and washing step was repeated once. The washed cells were subjected to fluorometer measurement to quantify the presence of FITC labeled lectin. The precision of the lectin assay and of the HMC assay were evaluated. In contrast to the HMC assay, the lectin assay results were linear with spoiled tissue dilution level. Because the HMC was by nature non-linear with high variability, a linearized HMC score was developed to compare with the lectin assay. The HMC scores of the two quality control laboratories which had the best precision among blind replicate measurements and the highest correlation between laboratories were averaged and used as the true Howard mold count for mold levels in the study. Four mold levels for C.herbarum and three mold levels for the remaining fungal species were regressed against the spoiled volume to develop linearized HMC models for each species. These models were then used to predict linearized HMC scores above the linear range for each species. The linearized HMC scores were then regressed against the lectin assay readings. The results show that the lectin assay gave generally comparable results to HMC in the linear range for each fungal organism.

L113 ANSWER 3 OF 16 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 2001-266373 [27] WPIX
DNN N2001-190479 DNC C2001-080736
TI Detection of proteins by using a protein fingerprinting system which comprises linearizing the protein, labeling a first amino acid residue type and detecting first and second residue types, useful in the diagnosis of cancer.
DC B04 D16 S03
IN **BRENT, R**; BURBULIS, I E; CARLSON, R H
PA (MOLE-N) MOLECULAR SCI INST INC
CYC 95
PI WO 2001025794 A2 20010412 (200127)* EN 55 G01N033-68
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2000077409 A 20010510 (200143) G01N033-68
EP 1218752 A2 20020703 (200251) EN G01N033-68
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
US 6569685 B1 20030527 (200337) G01N021-62
US 2003198940 A1 20031023 (200370) C12Q001-00
JP 2004506871 W 20040304 (200417) 86 G01N033-68
ADT WO 2001025794 A2 WO 2000-US26958 20000929; AU 2000077409 A AU 2000-77409 20000929; EP 1218752 A2 EP 2000-967167 20000929, WO 2000-US26958 20000929; US 6569685 B1 US 1999-412732 19991005; US 2003198940 A1 Div ex US 1999-412732 19991005, US 2003-444422 20030523; JP 2004506871 W WO 2000-US26958 20000929, JP 2001-528705 20000929
FDT AU 2000077409 A Based on WO 2001025794; EP 1218752 A2 Based on WO 2001025794; US 2003198940 A1 Div ex US 6569685; JP 2004506871 W Based on WO 2001025794
PRAI US 1999-412732 19991005; US 2003-444422 20030523
IC ICM C12Q001-00; G01N021-62; G01N033-68
ICS **C07K002-00**; C12M001-34; G01N021-63; G01N021-64; G01N033-58
AB WO 200125794 A UPAB: 20010518
NOVELTY - A new method (M1) for detecting proteins having at least two different types of residues comprises giving a detectable set of distinguishing ancillary properties (a 'fingerprint') to the proteins and then detecting the fingerprint by linearizing the protein, labeling the first type of residue and detecting first and second amino acid residues.

DETAILED DESCRIPTION - A new method (M1) for detecting proteins having at least two different types of residues comprises giving a detectable set of distinguishing ancillary properties (a 'fingerprint') to the proteins and then detecting the fingerprint by linearizing the protein, labeling the first type of residue and detecting first and second amino acid residues.

In detail, M1 comprises:

(a) linearizing the protein molecule with a denaturation means;

(b) labeling each of the first type of amino acid residue with a tag;

(c) detecting the fingerprint of the protein with a detection means, by detecting a first fingerprint constituent imparted by the tag and a second fingerprint constituent imparted by the second type of amino acid residue.

INDEPENDENT CLAIMS are also included for the following:

(1) identifying a protein molecule having at least two different amino acid residue types in a sample containing several proteins, by linearizing each protein as in M1 step (a), isolating the protein, conducting steps (b) and (c) of M1, and comparing the fingerprint obtained (optionally using a computer receiving signals from the detection means) to a library of fingerprints of known protein molecules;

(2) a library of fingerprint values of known proteins, listing the identity of the proteins and first and second (and optionally third) fingerprint constituents of each protein, being representative of the number and sequence of the first and second (and optionally third) types of amino acid residues respectively;

(3) characterizing protein molecules, by isolating the protein and using M1 which is modified such that first and second types of amino acid types are both labeled with different tags;

(4) protein molecules having an identifiable fingerprint, comprising two amino acid residue types each separately tagged, or three amino acid types (optionally including tryptophan), imparting up to six fingerprint constituents by using combinations of excitation and emitted radiations; and

(5) identifying a protein in a sample containing several proteins, following the method of (1) which is modified such that first and second residue types are both labeled with different tags.

USE - The method is useful to enable rapid identification of protein molecules, especially in biological samples e.g. plant, microorganism or animal (especially human) tissues or cells e.g. in clinical or research applications to identify aberrant or mutant forms of proteins involved in diseases such as cancers or inherited disorders such as cystic fibrosis and hemophilia. It also enables the production of a library of known proteins and their corresponding fingerprints, useful to identify unknown proteins in a sample.

Dwg.0/33

FS CPI EPI

FA AB; DCN

MC CPI: B04-B04H; B04-B04L; B04-N04; B11-C07B3; B11-C08; B12-K04A; D05-H09
EPI: S03-E14H

TECH UPTX: 20010518

TECHNOLOGY FOCUS - INSTRUMENTATION AND TESTING - Preferred Methods: The first amino acid residue type is preferably cysteine or lysine and the second preferably tryptophan (which self-fluoresces when exposed to electromagnetic excitation radiation of known wavelengths, enabling residues to be detected and distinguished from tagged residues).

The denaturation means is preferably a detergent (e.g. sodium dodecyl sulfate) or a chaotropic salt. Preferably, labeling is by a fluorescent dye and the detection means is primary excitation radiation which excites the dye. The detection means preferably further comprises a detector (e.g. a charge coupled device) sensitive to an emitted radiation of the dye. Alternatively, the detector means comprises a first source of electromagnetic radiation capable of exciting the second type of amino acid residue and a second source of electromagnetic radiation capable of

exciting the second type of amino acid residue.
The detector means further comprises a charged coupled device or camera/microscope positioned to detect emitted radiation or excitation radiation, respectively, from the first tag and second type of amino acid residue. Alternatively, the detector means comprises an atomic force microscope or a nuclear magnetic resonance apparatus. The atomic force microscope comprises a detector tip having a donor tag attached to it and the first tag is an acceptor tag that is excited upon coming into proximity to the donor tag.
The isolation means in method (1) preferably comprises a hydrodynamic focusing apparatus, electrophoresis gel, dilute solution or a separation plate opaque to light (e.g. formed of silicon or opaque plastic) having apertures (preferably 1-10 nm) in it.

ABEX UPTX: 20010518
EXAMPLE - No relevant example given.

```
L113 ANSWER 4 OF 16  WPIX  COPYRIGHT 2004 THE THOMSON CORP on STN
AN   2001-257787 [26]   WPIX
DNC  C2001-077654
TI   Use of leptin or a leptin homologue or derivative, optionally with a VEGF
     and/or angiogenesis inhibitor, for inhibiting endothelial cell
     proliferation and angiogenesis in the treatment of e.g. hemangioma, solid
     tumors and psoriasis.
DC   B05
IN   BARKAN, D; COHEN, B; RUBINSTEIN, M
PA   (YEDA) YEDA RES & DEV CO LTD
CYC  95
PI   WO 2001018040    A2 20010315 (200126)* EN   38    C07K014-00     <--
        RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
            NL OA PT SD SE SL SZ TZ UG ZW
         W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM
            DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC
            LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE
            SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
     AU 2000068620    A  20010410 (200137)             C07K014-00     <--
     EP 1210108       A2 20020605 (200238)  EN         A61K038-22
         R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
            RO SE SI
     NO 2002000920    A  20020503 (200238)             C07K000-00     <--
     BR 2000013778    A  20020514 (200240)             C07K014-00     <--
     KR 2002040781    A  20020530 (200276)             A61K038-18
     CN 1377277       A  20021030 (200314)             A61K038-22
     JP 2003508544    W  20030304 (200319)       38    A61K045-00
     ZA 2002001400    A  20030430 (200334)       56    A61K000-00
     MX 2002002448    A1 20020801 (200367)             A61K038-22
ADT  WO 2001018040 A2 WO 2000-IL525 20000904; AU 2000068620 A AU 2000-68620
     20000904; EP 1210108 A2 EP 2000-956758 20000904, WO 2000-IL525 20000904;
     NO 2002000920 A WO 2000-IL525 20000904, NO 2002-920 20020225; BR
     2000013778 A BR 2000-13778 20000904, WO 2000-IL525 20000904; KR 2002040781
     A KR 2002-702112 20020219; CN 1377277 A CN 2000-813748 20000904; JP
     2003508544 W WO 2000-IL525 20000904, JP 2001-522262 20000904; ZA
     2002001400 A ZA 2002-1400 20020219; MX 2002002448 A1 WO 2000-IL525
     20000904, MX 2002-2448 20020305
FDT  AU 2000068620 A Based on WO 2001018040; EP 1210108 A2 Based on WO
     2001018040; BR 2000013778 A Based on WO 2001018040; JP 2003508544 W Based
     on WO 2001018040; MX 2002002448 A1 Based on WO 2001018040
PRAI IL 1999-132312        19991010; IL 1999-131739        19990905
IC   ICM  A61K000-00; A61K038-18; A61K038-22; A61K045-00; C07K000-00;
          C07K014-00
     ICS  A61K031-185; A61K031-196; A61K031-522; A61K038-00; A61K048-00;
          A61P001-04; A61P003-00; A61P007-06; A61P009-00; A61P009-14;
          A61P015-00; A61P015-08; A61P017-00; A61P017-02; A61P017-06;
          A61P019-00; A61P019-02; A61P027-02; A61P027-06; A61P035-00;
```

A61P035-02; A61P035-04; A61P043-00
ICI A61K031:52, A61K038-22; A61K038-22, A61K038:17; A61K031:185, A61K038-22; A61K031:195, A61K038-22; A61K038-22, A61K038:19
AB WO 200118040 A UPAB: 20010515
NOVELTY - Use of leptin or a leptin homologue or derivative, optionally with an inhibitor of vascular endothelial growth factor (VEGF) action or of VEGF synthesis and/or an inhibitor of angiogenesis, in the preparation of a medicament for reversibly inhibiting endothelial cell proliferation is new.

DETAILED DESCRIPTION - Use of leptin or a leptin homologue or derivative, optionally with an inhibitor of VEGF action or of VEGF synthesis and/or an inhibitor of angiogenesis, in the preparation of a medicament for reversibly inhibiting endothelial cell proliferation is new.

INDEPENDENT CLAIMS are included for compositions:

(1) for reversibly inhibiting endothelial cell proliferation comprising leptin or a leptin homologue or derivative and optionally an inhibitor of VEGF action or of VEGF synthesis and/or an inhibitor of angiogenesis;

(2) for modulating angiogenic processes; and

(3) a mixture comprising leptin and a VEGF inhibitor.

ACTIVITY - Antiproliferative; cytostatic; vasotropic; antipsoriatic; antiangiogenesis; dermatological; cardiant; antiinflammatory; ophthalmological; vulnerary; antiarthritic; antiulcer; antibacterial; osteopathic; gynecological; antiinfertility; antipyretic; antiarteriosclerotic.

MECHANISM OF ACTION - Leptin induces the expression of the angiostatic factor angiopoietin-2 (Ang2).

USE - The leptin or a leptin homologue or derivative is used for reversibly inhibiting endothelial cell proliferation in mammals, modulating angiogenic processes and inhibiting angiogenesis (in combination with an angiogenesis inhibitor) (claimed), particularly in female reproductive organs, and for treating angiogenesis mediated diseases and processes, e.g. hemangioma, acoustic neuromas, neurofibromas, trachomas, pyrogenic granulomas, solid tumors, blood borne tumors, leukemia, metastasis, telangiectasia, psoriasis, scleroderma, myocardial angiogenesis, Crohn's disease, plaque neovascularization, coronary collaterals, cerebral collaterals, arteriovenous malformations, ischemic limb angiogenesis, myocardial angiogenesis, corneal diseases, rubeosis, neovascular glaucoma, diabetic retinopathy, retrolental fibroplasia, arthritis, psoriasis, diabetic neovascularization, macular degeneration, corneal graft rejection, wound healing, peptic ulcer, Helicobacter related diseases, fractures, keloids, vasculogenesis, hematopoiesis, ovulation, menstruation, placentation, hemophiliac joints, angiofibroma, wound granulation, cat scratch fever and Osler Webber-Syndrome. The leptin or a leptin homologue or derivative is also useful in the treatment of arteriosclerosis and hypertrophic scars. Compositions comprising leptin, a leptin homologue or derivative in combination with an inhibitor of VEGF action or synthesis, may also be used in the preparation of a medicament for regulating fertility or body weight (by inducing adipose tissue regression) in a mammal.

Murine leptin was (0.1-5 micrograms/gram) was injected intraperitoneally at time 0 and 9 hours into obese female mice lacking endogenous leptin. A noticeable weight loss was observed after 48 hours in mice receiving at least 2 x 1 micrograms/gram of leptin (65.4 plus or minus 0.5 g versus 62.7 plus or minus 1.0 g, n = 6). Abdominal fat was removed and fixed 24 hours and 48 hours after the first injection and blood vessels were counted after staining paraffin sections with antibodies to Factor VIII. A significant reduction in the number of blood vessels was observed (198 plus or minus 1 vessels per high power fields (HPFs, x 400) in control mice and 159 plus or minus 2.5 vessels per 5 HPFs in leptin-treated mice (2 x 1 micrograms/gram) at 24 hours and 106 plus or minus 7.5 vessels per 5 HPFs at 48 hours.

ADVANTAGE - Administration of leptin or leptin homologues or derivatives in combination with VEGF inhibitors and or other inhibitors of angiogenesis reduces abberant angiogenesis more effectively than a VEGF inhibitor or other angiogenesis inhibitor alone.
Dwg.0/7
FS CPI
FA AB; DCN
MC CPI: B04-H19; B04-K01J; B04-N02; B04-N02B; B14-A01; B14-C03; B14-C04; B14-C09; B14-E08; B14-F01; B14-F02; B14-H01; B14-L01; B14-L06; B14-N01; B14-N03; B14-N07; B14-N17; B14-P02
TECH UPTX: 20010515
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Compounds: The VEGF inhibitor is 3,7-dimethyl-1-propargylxanthine (DMPX), an A2 antagonist 7-(beta-hydroxyethyl)theophylline, 8-phenyltheophylline, the adenosine A2 receptor antagonist 8-(3-chlorostyryl)caffeine (CSC), theobromine, an antagonistic VEGF variant, the VEGF receptor sFLT-1, Tranilast, 8(3-oxo-4,5,6-trihydroxy-3h-xanthen-9-yl)-1-naphthoic acid, suramin or platelet factor-4.
Preferred Composition: The composition for modulating angiogenic processes inhibits angiogenesis (claimed).
ABEX UPTX: 20010515
WIDER DISCLOSURE - The use of expression vectors encoding leptin or leptin homologues, provided by gene therapy, in combination with inhibitors of VEGF action or production of other inhibitors of angiogenesis for regression of adipose tissues is also disclosed.

SPECIFIC COMPOUNDS - The use of leptin is specifically claimed.

ADMINISTRATION - Administration is by any known route of administration, e.g. intravenous, intraarterial, intraperitoneal, intramuscular, subcutaneous, intranasal, oral, topical, transdermal, intravaginal, intrauterine, intradermal, rectal, ophthalmic or pulmonary routes. The dosage of leptin or a leptin homologue or derivative is 0.5-10 mg/kg, administered from once per week to several times per day.

L113 ANSWER 5 OF 16 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 2000-072059 [06] WPIX
CR 1996-105852 [11]; 1997-512733 [47]
DNC C2000-020491
TI Population of Saccharomyces and/or mammalian cells comprising recombinant DNA encoding fusion proteins, useful for detecting protein interactions.
DC B04 D16
IN **BRENT, R**; JESSEN, T H; MCCOY, J M
PA (GEHO) GEN HOSPITAL CORP; (GEMY) GENETICS INST INC
CYC 1
PI US 6004746 A 19991221 (200006)* 24 C12Q001-68
ADT US 6004746 A CIP of US 1994-278082 19940720, US 1995-504538 19950720
PRAI US 1995-504538 19950720; US 1994-278082 19940720
IC ICM C12Q001-68
ICS C12N001-19; C12N005-16; C12Q001-00
AB US 6004746 A UPAB: 20020704
NOVELTY - A population of Saccharomyces and/or mammalian cells comprising recombinant DNA molecules encoding fusion proteins, each consisting of a candidate interactor peptide (I), a conformation- constraining protein (II) and a DNA binding moiety and/or gene activating moiety (III), is new.
USE - The cells are useful for detecting protein interactions. The cells may also be used in a method for identifying and purifying genes encoding a wide range of useful proteins based on their physical interaction with a second polypeptide.
Dwg.0/6
FS CPI
FA AB; DCN
MC CPI: B04-C01D; B04-C01E; B04-E02; B04-E04; B04-F0200E; B04-F09C0E;

B04-N02A; B11-C08E; B12-K04E; D05-H09; D05-H12C; D05-H12D5;
D05-H14A2; D05-H14B2; D05-H17C

TECH UPTX: 20000203

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Cells: (II) is heterologous to (I). (I) has reduced structural flexibility due to covalent bonding of both the amino and carboxy termini of the peptide to heterologous (II). There are at least 100 different recombinant DNA molecules encoding (I) in the population. (II) is **thioredoxin** or a **thioredoxin** -like molecule characterized by:

(i) having a three-dimensional structure similar to that of Escherichia coli **thioredoxin**; and

(ii) containing an active site loop functionally and structurally equivalent to the double cysteine- containing active site loop of E. coli **thioredoxin.**

(I) is fused within the active site loop of (II). (I) physically interacts with a second recombinant protein. (I) has a recombinantly-introduced cysteine residue at its amino terminus and at its carboxy terminus.

ABEX UPTX: 20000203

WIDER DISCLOSURE - Also disclosed as new are the following:

(1) libraries encoding conformationally-constrained proteins; and

(2) conformationally-constrained proteins selected from one of twelve given in the specification e.g. LVCKSYRLDWEAGALFRSLF, MVVAAEAVRTVLLADGGDVT, PNWPHQLRVGRVLWERLSFE.

EXAMPLE - None given.

L113 ANSWER 6 OF 16 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

AN 1999-385092 [32] WPIX

DNN N1999-288429 DNC C1999-113187

TI Two-bait interaction trap for detection of protein-protein interactions.

DC B04 D16 S03

IN **BRENT, R**; LOK, W L; MENDELSOHN, A R; XU, C W; XU, W C; XU, C

PA (GEHO) GEN HOSPITAL CORP; (BREN-I) BRENT R; (LOKW-I) LOK W L; (MEND-I) MENDELSOHN A R; (XUCW-I) XU C W

CYC 83

```
PI   WO 9924455      A1 19990520 (199932)* EN   51    C07H021-04
        RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
            OA PT SD SE SZ UG ZW
         W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE
            GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG
            MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG
            UZ VN YU ZW
     AU 9913855      A  19990531 (199941)             C07H021-04
     EP 1042351      A1 20001011 (200052)  EN         C07H021-04
         R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE
     BR 9812783      A  20001010 (200055)             C07H021-04
     US 6171792      B1 20010109 (200104)             C12Q001-00
     CZ 2000001594   A3 20010314 (200117)             C07H021-04
     CN 1285846      A  20010228 (200131)             C07H021-04
     HU 2000004415   A2 20010428 (200131)             C07H021-04
     KR 2001024604   A  20010326 (200161)             C07H021-04
     MX 2000004451   A1 20001101 (200163)             C07H021-04
     JP 2001522598   W  20011120 (200204)       54    C12N001-19
     US 2002072088   A1 20020613 (200243)#            C12P021-06     <--
     AU 748358       B  20020606 (200249)             C07H021-04
```

ADT WO 9924455 A1 WO 1998-US23696 19981106; AU 9913855 A AU 1999-13855 19981106; EP 1042351 A1 EP 1998-957647 19981106, WO 1998-US23696 19981106; BR 9812783 A BR 1998-12783 19981106, WO 1998-US23696 19981106; US 6171792 B1 Provisional US 1997-65273P 19971110, US 1998-189653 19981110; CZ 2000001594 A3 WO 1998-US23696 19981106, CZ 2000-1594 19981106; CN 1285846 A CN 1998-813011 19981106; HU 2000004415 A2 WO 1998-US23696 19981106, HU 2000-4415 19981106; KR 2001024604 A KR 2000-705038 20000509; MX 2000004451 A1 MX 2000-4451 20000509; JP 2001522598 W WO 1998-US23696 19981106, JP

2000-520463 19981106; US 2002072088 A1 Cont of US 1998-189653 19981110, US 2001-757309 20010109; AU 748358 B AU 1999-13855 19981106
FDT AU 9913855 A Based on WO 9924455; EP 1042351 A1 Based on WO 9924455; BR 9812783 A Based on WO 9924455; CZ 2000001594 A3 Based on WO 9924455; HU 2000004415 A2 Based on WO 9924455; JP 2001522598 W Based on WO 9924455; AU 748358 B Previous Publ. AU 9913855, Based on WO 9924455
PRAI US 1997-65273P 19971110; US 1998-189653 19981110;
US 1997-65273 19971011; US 2001-757309 20010109
IC ICM C07H021-04; C12N001-19; **C12P021-06**; C12Q001-00
ICS C12N001-15; C12N005-10; C12N015-09; **C12P021-04**; C12Q001-68; G01N033-53; G01N033-566
AB WO 9924455 A UPAB: 19990813
NOVELTY - A two-bait interaction trap for detection of protein-protein interactions is new.

DETAILED DESCRIPTION - Detecting a protein-protein interaction comprises:

(a) providing a host cell which contains:

(i) first and second reporter genes (R1 and R2), each independently operably linked to a DNA sequence comprising a protein binding site (PBS1 and PBS2, respectively);

(ii) first and second fusion genes each expressing a fusion protein (F1 and F2), where the proteins comprise, independently, a protein covalently bonded to a binding moiety capable of specifically binding to the respective protein binding sites PBS1 and PBS2; and

(iii) a third fusion gene expressing a third fusion protein (F3), comprising a third protein covalently bonded to a gene activating moiety;

(b) measuring expression output of R1 and R2 as a measure of interaction between F1 and F3 or F2 and F3, respectively; and

(c) interpreting the expression output results, where:

(i) increased output of R1 and R2 indicates interaction of F3 with both F1 and F2;

(ii) increased output of R1, but not R2, indicates interaction of F3 with F1 but not F2;

(iii) increased output of R2, but not R1, indicates interaction of F3 with F2 but not F1;

(iv) no change in output in either R1 or R2 indicates that F3 does not interact with F1 or F2.

INDEPENDENT CLAIMS are also included for the following:

(1) detecting a protein that mediates a change in the state of another protein;

(2) a cell comprising R1, R2 and F1, F2 and F3 as above;

(3) detecting whether a candidate protein interacts with a transcriptional activator; and

(4) a reporter gene comprising a tetracycline operator operably linked to a gene encoding a detectable product.

USE - The detection systems are useful for registering complex protein interactions and functional relationships.

ADVANTAGE - This two-bait system, especially when combined with existing one bait systems, extends the scope of yeast interaction technology to analyze the function of genes in pathways.

DESCRIPTION OF DRAWING(S) - Schematic illustration of a two-bait interaction trap using LexA and TetR DNA binding moieties and the tetracycline repressor of bacterial transposon Tn10.

Dwg.1A-C/6
FS CPI EPI
FA AB; GI; DCN
MC CPI: B04-E02; B04-F01; B04-N02; B04-N03; B04-N04; B11-C08; B12-K04; D05-H09; D05-H12C; D05-H14A2; D05-H14B2; D05-H17C
EPI: S03-E14H4
TECH UPTX: 19990813
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Methods: The expression output of R1 and R2 is compared with expression results measured in comparison host cells (controls). At least one of R1 and R2 may be reduced

in expression level. One of the PBS is a tetracycline operator. R1 or R2 is URA3 or lacZ. One of R1 or R2 produce a signal that is received and detected by a second cell. R1 and R2 may be expressed simultaneously. The first and second proteins contained in F1 and F2 are allelic variants. The method is carried out in a mammalian cell or preferably in a yeast cell.

An alternative method for detecting a protein that mediates a change in the state of another protein comprises using a one-bait interaction system where interaction of a first and second protein (expressed by a first fusion gene and a second fusion gene, respectively) results in expression of the reporter gene. Introduction of a third gene expressing a third protein into the system and measuring any change in the expression of the reporter gene indicates that the third protein mediates a change in the first or second protein leading to an alteration in the ability of the first and second proteins to interact.

Optionally, the method may include providing a second host cell comprising a first fusion gene which expresses a first fusion protein, a second fusion gene which expresses a second fusion protein and a third gene which expresses a third protein. The first and second proteins are allowed to interact in the presence of the third protein. The expression of the reporter gene in the second host cell is measured, where a change in the reporter gene expression when compared with the first and second host cell is an indication that the third protein mediates a change in the state of the first and second protein. The change in state is a conformational change and the protein exhibiting this change is a Ras protein. Expression of the first fusion protein and the third protein occurs in response to an extracellular stimulus. The reporter gene produces a signal that is received and detected by a second cell.

Detecting whether a candidate protein interacts with a transcriptional activator uses a modified yeast one-bait system, where the reporter gene, URA3, can be reduced in expression level, especially by 6-azauracil. The yeast contains a first fusion gene expressing F1 and a second fusion gene expressing F2. Detection of an increase in expression of the reporter gene is an indication of an interaction between the candidate protein and the transcriptional activator.

The two-bait interaction trap system relies on logical operations. The two contact relationships (and the output of the corresponding reporters) are expressed as Boolean variables, A1 and A2. There are 16 possible operations on these variables, four of which were registered in these cells. These operations are referred to as And, Nor and the two discrimination operations, logic state 1 (Ls 1) and logic state 2 (Ls2). Ls1 and Ls2 are considered to be useful operations for determining protein function.

Preferred Reporter Gene: The detectable product is URA3 or lacZ.

ABEX UPTX: 19990813

EXAMPLE - A two-bait cell that contained TetR-RasV12 and LexA-RasA15 was used to isolate members of a peptide aptamer library that interacted specifically with RasV12. URA+ library transformants were screened for lacZ- cells, which presumably contained aptamers that did not interact with LexA-RasA15. Plasmids encoding aptamers were then rescued from these lacZ+ cells and their phenotypes reconfirmed. Using this system, two discriminatory aptamers, Pep22 and Pep104, were identified. Pep22 interacted with both RasV12 and RasA15, whereas, by contrast, Pep104 interacted only with RasV12. In particular, the Pep22-containing cell grew on Ura- medium and was blue on X-gal medium. The Pep104-containing cell grew on Ura- medium but was white on X-gal medium. These results demonstrated the utility of this system in selection of specific peptide aptamers. For Pep22, the second bait increased the selectivity of the system by eliminating potential false positives that might arise from artifactual activation of a single reporter. For Pep104, the second bait allowed detection of aptamers specific for an allelic form of the protein active in signal transduction. The sequences of Pep22 and Pep104 are DMDWFFRFYASVSRLFRHLH and FWQATLRLVSDKLILLYPDP, respectively.

L113 ANSWER 7 OF 16 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 1997-512733 [47] WPIX
CR 1996-105852 [11]; 2000-072059 [06]
DNN N1997-426765 DNC C1997-163732
TI New trap system for detecting protein interactions - comprises a reporter gene linked to a DNA-binding-protein recognition site and fusion proteins to test for interactions.
DC B04 D16 S03
IN **BRENT, R**; JESSEN, T H; MCCOY, J M; XU, C W
PA (GEHO) GEN HOSPITAL CORP; (GEMY) GENETICS INST INC; (BREN-I) BRENT R; (JESS-I) JESSEN T H; (MCCO-I) MCCOY J M; (XUCW-I) XU C W
CYC 20
PI WO 9738127 A1 19971016 (199747)* EN 89 C12Q001-00
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: JP
EP 904402 A1 19990331 (199917) EN
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE
JP 2000508174 W 20000704 (200037) 80 C12N015-09
US 6399296 B1 20020604 (200242) C12Q001-68
US 2003113749 A1 20030619 (200341) C12Q001-68
ADT WO 9738127 A1 WO 1997-US5793 19970409; EP 904402 A1 EP 1997-917897 19970409, WO 1997-US5793 19970409; JP 2000508174 W JP 1997-536441 19970409, WO 1997-US5793 19970409; US 6399296 B1 CIP of US 1994-278082 19940720, CIP of US 1995-504538 19950720, US 1996-630052 19960409; US 2003113749 A1 CIP of US 1994-278082 19940720, CIP of US 1995-504538 19950720, Cont of US 1996-630052 19960409, US 2002-162538 20020604
FDT EP 904402 A1 Based on WO 9738127; JP 2000508174 W Based on WO 9738127; US 6399296 B1 CIP of US 6004746; US 2003113749 A1 CIP of US 6004746, Cont of US 6399296
PRAI US 1996-630052 19960409; US 1994-278082 19940720;
US 1995-504538 19950720; US 2002-162538 20020604
REP 3.Jnl.Ref; US 5283173
IC ICM C12N015-09; C12Q001-00; C12Q001-68
ICS **C07K007-08**; **C07K014-00**; **C07K019-00**;
C12N001-19; C12N001-21; C12N005-10; **C12P021-00**; C12Q001-02;
G01N033-53; G01N033-567
AB WO 9738127 A UPAB: 20030919
A novel method for determining whether a first protein (P1) is capable of physically interacting with a second protein (P2), comprises: (a) providing a host cell which contains: (i) a reporter gene operably linked to a DNA-binding-protein (DBP) recognition site; (ii) a first fusion gene which expresses a first fusion protein (FP1) comprising P1 covalently bonded to a binding moiety which is capable of specifically binding to the DBP recognition site; (iii) a second fusion gene which expresses a second fusion protein (FP2) comprising P2 covalently bonded to a gene activating moiety and being conformationally-constrained; and (b) measuring expression of the reporter gene as a measure of an interaction between P1 and P2.

USE - The methods can be used to identify agonists or antagonists for use as therapeutic molecules or for the design of simple organic molecule mimetics. The method is specifically used to detect an interacting protein in a population of proteins or to identify a candidate interactor (claimed).

ADVANTAGE - The use of conformationally constrained proteins can provide for tertiary structural analysis, thus facilitating the design of simple organic molecule mimetics with improved pharmacological properties. They can also protect proteins from cellular degradation and/or increase the protein's solubility, and/or otherwise alter the capacity of the candidate interactor to interact.

Dwg.0/10
FS CPI EPI
FA AB

MC CPI: B04-E02F; B04-F01; B04-N04; B11-C08; B12-K04; D05-H09; D05-H12A;
D05-H17A6; D05-H18
EPI: S03-E14H4

L113 ANSWER 8 OF 16 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 1996-105852 [11] WPIX
CR 1997-512733 [47]; 2000-072059 [06]
DNN N1996-088666 DNC C1996-033511
TI Interaction trap systems using conformationally-constrained proteins - useful for detection of protein interactions and for identification and isolation of interacting proteins.
DC B04 D16 S03
IN **BRENT, R**; JESSEN, T H; MCCOY, J M; XU, C; XU, C W
PA (GEHO) GEN HOSPITAL CORP; (GEMY) GENETICS INST INC; (GEMY) GENETICS INST LLC
CYC 19
PI WO 9602561 A1 19960201 (199611)* EN 73 C07H021-04
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: JP
EP 773952 A1 19970521 (199725) EN C07H021-04
R: AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE
JP 10504713 W 19980512 (199829) 65 C12N015-09
US 6242183 B1 20010605 (200133) C12Q001-68
EP 773952 B1 20031112 (200380) EN C07H021-04
R: AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE
DE 69532127 E 20031218 (200407) C07H021-04
EP 1405911 A1 20040407 (200425) EN C12N015-11
R: AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE
ES 2210306 T3 20040701 (200444) C07H021-04
ADT WO 9602561 A1 WO 1995-US9307 19950720; EP 773952 A1 EP 1995-928118 19950720, WO 1995-US9307 19950720; JP 10504713 W WO 1995-US9307 19950720, JP 1996-505277 19950720; US 6242183 B1 Cont of US 1994-278082 19940720, US 1999-249458 19990212; EP 773952 B1 EP 1995-928118 19950720, WO 1995-US9307 19950720; DE 69532127 E DE 1995-632127 19950720, EP 1995-928118 19950720, WO 1995-US9307 19950720; EP 1405911 A1 Div ex EP 1995-928118 19950720, EP 2003-21647 19950720; ES 2210306 T3 EP 1995-928118 19950720
FDT EP 773952 A1 Based on WO 9602561; JP 10504713 W Based on WO 9602561; EP 773952 B1 Based on WO 9602561; DE 69532127 E Based on EP 773952, Based on WO 9602561; EP 1405911 A1 Div ex EP 773952; ES 2210306 T3 Based on EP 773952
PRAI US 1994-278082 19940720; US 1999-249458 19990212
REP 05Jnl.Ref; US 5270181; US 5283173
IC ICM C07H021-04; C12N015-09; C12N015-11; C12Q001-68
ICS A61K045-00; **C07K007-08**; **C07K014-00**;
C07K014-47; **C07K019-00**; C12N001-19; C12N005-10;
C12N009-02; C12N015-62; **C12P021-02**; C12Q001-00; G01N033-53;
G01N033-566; G01N033-68
AB WO 9602561 A UPAB: 20040712
Determining whether a 1st protein (A) is capable of physically interacting with a 2nd protein (B) comprises providing a host cell which contains: (i) a reporter gene operably linked to a DNA-binding-protein recognition site; (ii) a 1st fusion gene which expresses (A), comprising a 1st protein covalently bonded to a binding moiety which is capable of specifically binding to the DNA-binding-protein recognition site; and (iii) a 2nd fusion gene which expresses (B), comprising a 2nd protein covalently bonded to a gene activating moiety and being conformationally-constrained, and measuring expression of the reporter gene as a measure of an interaction between (A) and (B). The same system is applied in: (i) detecting an interacting protein in a population of proteins; (ii) identifying a candidate interactor; and (iii) assaying an interaction between (A) and (B).

USE - The new method provides an interaction trap system for the identification and analysis of conformationally-constrained proteins, that

either physically interact with a 2nd protein of interest or that
antagonise or agonise such an interaction.
ADVANTAGE - The system provides rapid and inexpensive methods, having very general utility for identifying and purifying genes encoding a wide range of useful proteins based on the protein's physical interaction with a 2nd polypeptide.
Dwg.0/6

```
FS   CPI EPI
FA   AB
MC   CPI: B04-E03; B04-F01; B04-F0100E; B04-N04; B11-C08E; B12-K04; D05-H09;
          D05-H14
     EPI: S03-E14H

L113 ANSWER 9 OF 16  WPIX  COPYRIGHT 2004 THE THOMSON CORP on STN
AN   1995-311811 [41]    WPIX
CR   1994-093835 [12]
DNC  C1995-138890
TI   New DNA encoding interferon alpha/beta binding protein - useful for
     treating auto immune diseases, inflammation and toxicity due to interferon
     treatment.
DC   B04 D16
IN   COHEN, B; NOVICK, D; RUBINSTEIN, M
PA   (YEDA) YEDA RES & DEV CO LTD; (COHE-I) COHEN B
CYC  27
PI   AU 9511416       A  19950817 (199541)*      82    C12N015-12
     NO 9500420       A  19950808 (199541)             C12N015-12
     CA 2141747       A  19950808 (199544)             C12N015-20
     FI 9500516       A  19950808 (199544)             C07K000-00      <--
     EP 676413        A2 19951011 (199545)  EN   35    C07K014-715     <--
         R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
     JP 07298886      A  19951114 (199603)        1    C12N015-09
     ZA 9500968       A  19951227 (199605)       82    C12N000-00
     EP 676413        A3 19960403 (199625)             C12N015-12
     CN 1109505       A  19951004 (199734)             C12N015-19
     AU 688430        B  19980312 (199822)             C12N015-12
     US 5821078       A  19981013 (199848)             C12N015-12
     MX 197237        B  20000628 (200133)             C12N015-012
     US 6458932       B1 20021001 (200268)             C07K014-715     <--
     RU 2232811       C2 20040720 (200455)             C12N015-12
ADT  AU 9511416 A AU 1995-11416 19950127; NO 9500420 A NO 1995-420 19950206; CA
     2141747 A CA 1995-2141747 19950203; FI 9500516 A FI 1995-516 19950206; EP
     676413 A2 EP 1995-101560 19950206; JP 07298886 A JP 1995-43539 19950207;
     ZA 9500968 A ZA 1995-968 19950207; EP 676413 A3 EP 1995-101560 19950206;
     CN 1109505 A CN 1995-100194 19950207; AU 688430 B AU 1995-11416 19950127;
     US 5821078 A CIP of US 1993-115741 19930903, US 1995-385191 19950207; MX
     197237 B MX 1995-825 19950206; US 6458932 B1 CIP of US 1993-115741
     19930903, Div ex US 1995-385191 19950207, US 1995-472402 19950607; RU
     2232811 C2 RU 1995-101848 19950206
FDT  AU 688430 B Previous Publ. AU 9511416; US 6458932 B1 Div ex US 5821078
PRAI IL 1994-108584       19940207; IL 1992-103052       19920903;
     IL 1993-106591       19930804
REP  2.Jnl.Ref; EP 588177; WO 9105862; WO 9218626
IC   ICM  C07K000-00; C07K014-715; C12N000-00; C12N015-012;
          C12N015-09; C12N015-12; C12N015-19; C12N015-20
     ICS  A61K038-00; A61K038-16; A61K038-17; A61K038-21; C07H021-04;
          C07K001-22; C07K007-15; C07K014-555;
          C07K016-18; C07K016-28; C07K019-00;
          C12N001-20; C12N005-10; C12N005-16; C12N015-62; C12N015-63;
          C12N015-70; C12N015-79; C12N015-81; C12P021-00;
          C12P021-04; G01N033-53; G01N033-566; G01N033-577
ICA  A61K039-395
ICI  C12P021-00, C12R001:91
AB   AU    9511416 A UPAB: 20040826
```

A novel DNA molecule (I) encodes an IFN- alpha / beta binding protein selected from IFNAB-BPI, IFNAB-BPII, their precursors, fused proteins and muteins of TFNAB-BPI or IFNAB-BPII, their functional derivs. or their active fractions.

USE - (I) may be used for production of (II) by recombinant methods. (II) are useful for treatment of autoimmune diseases or other inflammations, for treatment of toxicity caused by admin. of interferon alpha or beta , and for treatment of juvenile diabetes, lupus erythematosus or AIDS. Non-therapeutic applications include in the purificn. of type I interferon species. The antibodies may be used to quantitatively or qualitatively detect (II) in a sample or to detect the presence of cells which express (II).

Dwg.0/10

FS CPI
FA AB
MC CPI: B04-E02F; B04-G01; B04-N03; B14-C03; B14-G02D; D05-C12; D05-H12A; D05-H12E; D05-H14B2; D05-H17A6

L113 ANSWER 10 OF 16 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 1994-264033 [32] WPIX
DNC C1994-120832
TI Max-interacting polypeptide and DNA encoding them - used as anticancer agents and to screen for agents which inhibit cellular proliferation.
DC B04 D16
IN **BRENT, R**; ZERVOS, A S
PA (GEHO) GEN HOSPITAL CORP; (BREN-I) BRENT R; (ZERV-I) ZERVOS A S
CYC 20

PI							
WO 9417101	A1	19940804	(199432)*	EN	57	C07K013-00	<--
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE							
W: CA JP							
EP 681588	A1	19951115	(199550)	EN		C07K013-00	<--
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE							
US 5512473	A	19960430	(199623)		25	C12N001-21	
JP 08509118	W	19961001	(199705)		58	C12N015-09	
US 5780262	A	19980714	(199835)			C12N005-10	
US 5852169	A	19981222	(199907)			C07K014-47	<--

ADT WO 9417101 A1 WO 1993-US12643 19931229; EP 681588 A1 WO 1993-US12643 19931229, EP 1994-907772 19931229; US 5512473 A US 1993-11398 19930129; JP 08509118 W WO 1993-US12643 19931229, JP 1994-517027 19931229; US 5780262 A Cont of US 1993-11398 19930129, US 1995-464051 19950605; US 5852169 A Div ex US 1993-11398 19930129, US 1995-462498 19950605
FDT EP 681588 A1 Based on WO 9417101; JP 08509118 W Based on WO 9417101; US 5780262 A Cont of US 5512473; US 5852169 A Div ex US 5512473
PRAI US 1993-11398 19930129; US 1995-464051 19950605; US 1995-462498 19950605
REP 04Jnl.Ref
IC ICM **C07K013-00**; **C07K014-47**; C12N001-21; C12N005-10; C12N015-09
ICS C12N015-12; C12N015-54; C12N015-63; **C12P021-02**; **C12P021-08**; C12Q001-00; C12Q001-18
ICA C12Q001-48
ICI **C12P021-02**, C12R001:91
AB WO 9417101 A UPAB: 19940928

A pure preparation of a Max-interacting (Mxi) polypeptide is claimed.

Also claimed are: (1) purified DNA comprising a sequence encoding a Mxi polypeptides; (2) a vector and a cell containing this DNA; and (3) a purified antibody specific for a Mxi polypeptide.

The Mxi polypeptide is mammalian, pref. human, and is especially Mxi1 or Mxi2. The Mxi polypeptide is encoded by a 2417 (Mxi1) or 1200 (Mxi2) base sequence (given in the specification).

USE - Mxi polypeptide can be used to inhibit mammalian cell proliferation. Detection of Mxi gene expression and comparison of the change in expression with a wild type sample can also be used to detect

malignant cells in biological samples. Agents which inhibit cellular proliferation can also be identified by mixing them with a Mxi polypeptide and measuring Mxi activity. A change in activity is indicative of a proliferation-inhibitory cpd. The antibodies can be used to monitor the levels of Mxi polypeptides produced by a mammal. Mxi polypeptides are pref. delivered as therapeutic agents as sense or antisense RNA prods. by expression in a retroviral vector, e.g. to the bone marrow. The Mxi polypeptide is also useful for identifying the part of a mammalian cell where important cell division control functions occur.
Dwg.0/7

FS CPI
FA AB
MC CPI: B04-E03B; B04-E08; B04-F0100E; B04-G02; B04-N02A; B12-K04A1;
B14-H01B; D05-H11; D05-H12A; D05-H12E; D05-H14
ABEQ US 5512473 A UPAB: 19960610
Purified DNA comprising a sequence encoding a human Mxi1 polypeptide is new.
Dwg.0/7

L113 ANSWER 11 OF 16 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 1994-167458 [20] WPIX
DNC C1994-076792
TI Determining whether protein interacts with known protein, especially with Cdc2
-
useful to detect cancer and to develop anticancer agents.
DC B04 D16
IN **BRENT, R**; GOLEMIS, E; GYURIS, J
PA (GEHO) GEN HOSPITAL CORP
CYC 20
PI WO 9410300 A1 19940511 (199420)* EN 80 C12N015-10
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: CA JP
EP 672131 A1 19950920 (199542) EN C12N015-10
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
EP 672131 A4 19951115 (199626) C12N015-10
JP 08506480 W 19960716 (199650) 81 C12N015-09
US 5580736 A 19961203 (199703) 40 C12Q001-68
US 5786169 A 19980728 (199837) C12P021-06 <--
EP 1362913 A2 20031119 (200377) EN C12N015-10
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
EP 672131 B1 20031217 (200404) EN C12N015-12
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
DE 69333366 E 20040129 (200416) C12N015-12
JP 3537141 B2 20040614 (200439) 42 C12N015-09
ADT WO 9410300 A1 WO 1993-US10069 19931020; EP 672131 A1 EP 1993-900596 19931020, WO 1993-US10069 19931020; EP 672131 A4 EP 1993-900596 ; JP 08506480 W WO 1993-US10069 19931020, JP 1994-511161 19931020; US 5580736 A Cont of US 1992-969038 19921030, US 1995-370225 19950109; US 5786169 A Cont of US 1992-969038 19921030, Div ex US 1995-370225 19950109, US 1995-461859 19950605; EP 1362913 A2 Div ex EP 1993-900596 19931020, EP 2003-17549 19931020; EP 672131 B1 EP 1993-900596 19931020, WO 1993-US10069 19931020, Related to EP 2003-17549 19931020; DE 69333366 E DE 1993-633366 19931020, EP 1993-900596 19931020, WO 1993-US10069 19931020; JP 3537141 B2 WO 1993-US10069 19931020, JP 1994-511161 19931020
FDT EP 672131 A1 Based on WO 9410300; JP 08506480 W Based on WO 9410300; US 5786169 A Div ex US 5580736; EP 1362913 A2 Div ex EP 672131; EP 672131 B1 Related to EP 1362913, Based on WO 9410300; DE 69333366 E Based on EP 672131, Based on WO 9410300; JP 3537141 B2 Previous Publ. JP 08506480, Based on WO 9410300
PRAI US 1992-969038 19921030; US 1995-370225 19950109;
US 1995-461859 19950605
REP 08Jnl.Ref; 3.Jnl.Ref
IC ICM C12N015-09; C12N015-10; C12N015-12; **C12P021-06**; C12Q001-68

ICS A61K038-00; **C07K014-39**; **C07K014-47**;
C07K016-14; **C07K016-18**; **C07K016-40**;
C12N009-16; C12N015-00; C12N015-62; C12N015-63; C12N015-81;
C12P021-08; C12Q001-02; G01N033-53
ICA C12N001-19; **C12P021-02**
AB WO 9410300 A UPAB: 19940705
Determining whether a first protein (FP) is capable of physically interacting with a second protein (SP) comprises: (a) providing a host cell which contains (i) a reporter gene operably linked to a protein binding site, (ii) a first fusion gene which expresses a first fusion protein which comprises FP covalently bonded to a binding moiety which is capable of specifically binding to the protein binding site; and (iii) a second fusion gene which expresses a second fusion protein comprising SP covalently bonded to a weak gene activating moiety; and (b) measuring expression of the reporter gene as a measure of an interaction between FP and SP. The SP is pref. involved in control of eukaryotic cell division and is especially Cdc2. Also new is: a pure preparation of Cdi1 polypeptide (I).

Specifically Cdi1 was identified using the new method. Cdi1 interacts with Cdc2 and appears to be a good candidate for an anti-cancer therapeutic. The method could also be used to screen for cpds. which interfere with the Cdi1-Cdc2 interaction. Cdi1 polypeptide is also useful in detection or monitoring of cancerous conditions (claimed).

USE/ADVANTAGE - The method is rapid and inexpensive and has general use for identifying and purifying a wide range of useful proteins based on the proteins physical interaction with a polypeptide of known-diagnostic and therapeutic usefulness. Components of the system can be readily modified to facilitate detection of protein interactions of widely varying affinity (e.g. by using reporter genes which differ quantitatively in their sensitivity to a protein interaction).
Dwg.0/10
FS CPI
FA AB
MC CPI: B04-C01; B04-E02F; B04-E08; B04-F09C0E; B04-G01; B04-N02; B12-K04;
D05-H09; D05-H11; D05-H12A; D05-H17A; D05-H17C
ABEQ US 5580736 A UPAB: 19970115
A novel method for determining whether a first protein is capable of physically interacting with a second protein, comprises:

(a) providing a host cell which contains:

(i) a reporter gene operably linked to a DNA sequence comprising a protein binding site;

(ii) a first fusion gene which expresses a first fusion protein, the first fusion protein comprising the first protein covalently bonded to a binding moiety which is capable of specifically binding to the protein binding site; and

(iii) a second fusion gene which expresses a second fusion protein, the second fusion protein comprising the second protein covalently bonded to a weak gene activating moiety;

(b) allowing the first protein and the second protein to interact; and

(c) measuring expression of the reporter gene as a measure of the interaction between the first and second proteins.
Dwg.0/10

L113 ANSWER 12 OF 16 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 1994-093835 [12] WPIX
CR 1995-311811 [41]
DNC C1994-042964
TI New protein binding interferon alpha and beta - for treating conditions, e.g. diabetes or graft rejection, associated with abnormal interferon expression, also new DNA vectors etc.
DC B04 D16
IN NOVICK, D; RUBINSTEIN, M; **COHEN, B**

```
PA    (YEDA) YEDA RES & DEV CO LTD; (NOVI-I) NOVICK D
CYC   22
PI    EP 588177         A2 19940323 (199412)* EN    37     C12N015-12
          R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
      AU 9346096        A  19940310 (199415)               C07K015-05     <--
      CA 2105449        A  19940304 (199420)               C12N015-20
      JP 06220100       A  19940809 (199436)        17     C07K015-26     <--
      ZA 9306442        A  19950125 (199510)        53     C12N000-00
      EP 588177         A3 19940817 (199530)               C12N015-12
      AU 674523         B  19970102 (199709)               C07K015-06     <--
      US 5821078        A  19981013 (199848)               C12N015-12
      EP 588177         B1 20000126 (200010)  EN           C12N015-12
          R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
      DE 69327693       E  20000302 (200018)               C12N015-12
      ES 2142840        T3 20000501 (200028)               C12N015-12
      US 6458932        B1 20021001 (200268)               C07K014-715    <--
      JP 2004254695     A  20040916 (200461)        27     C12N015-09
ADT   EP 588177 A2 EP 1993-114084 19930902; AU 9346096 A AU 1993-46096 19930902;
      CA 2105449 A CA 1993-2105449 19930902; JP 06220100 A JP 1993-243987
      19930902; ZA 9306442 A ZA 1993-6442 19930901; EP 588177 A3 EP 1993-114084
      19930902; AU 674523 B AU 1993-46096 19930902; US 5821078 A CIP of US
      1993-115741 19930903, US 1995-385191 19950207; EP 588177 B1 EP 1993-114084
      19930902; DE 69327693 E DE 1993-627693 19930902, EP 1993-114084 19930902;
      ES 2142840 T3 EP 1993-114084 19930902; US 6458932 B1 CIP of US 1993-115741
      19930903, Div ex US 1995-385191 19950207, US 1995-472402 19950607; JP
      2004254695 A Div ex JP 1993-243987 19930902, JP 2004-90279 20040325
FDT   AU 674523 B Previous Publ. AU 9346096; DE 69327693 E Based on EP 588177;
      ES 2142840 T3 Based on EP 588177; US 6458932 B1 Div ex US 5821078
PRAI  IL 1993-106591          19930804; IL 1992-103052        19920903;
      IL 1994-108584          19940207
REP   No-SR.Pub; 3.Jnl.Ref; EP 369877; FR 2657881
IC    ICM  C07K014-715; C07K015-05; C07K015-06;
           C07K015-26; C12N000-00; C12N015-09; C12N015-12; C12N015-20
      ICS  A61K037-02; A61K037-66; A61K038-00; A61K038-17; A61K039-395;
           A61P029-00; A61P037-02; C07K001-22; C07K003-02;
           C07K003-20; C07K007-15; C07K013-00;
           C07K014-47; C07K014-555; C07K019-00;
           C12N001-15; C12N001-19; C12N001-21; C12N005-10; C12N005-20;
           C12N015-21; C12N015-22; C12N015-62; C12P021-02;
           C12P021-04; C12P021-08
AB    EP    588177 A UPAB: 20040923
      IFN (interferon)-alpha/beta binding protein (I), its mutants or fusion
      proteins, their salts, functional derivs. and active fractions are new.
           USE - (I) inhibits the biological (antiviral) activity of IFN-alpha2;
      -alphaB; -alphaC or -beta (it may be a receptor component or the soluble
      form of a new receptor). (I) can be used to modulate aberrant expression
      of IFN e.g. in type I diabetes, auto-immune disease, graft rejection,
      AIDS, etc.
      Dwg.0/10
FS    CPI
FA    AB; DCN
MC    CPI: B04-E02F; B04-E08; B04-F02; B04-G02; B04-K01K; B04-N02; B14-G01B;
           B14-G02C; B14-G02D; B14-S04; D05-H11; D05-H12A; D05-H12E; D05-H14;
           D05-H15

L113 ANSWER 13 OF 16  WPIX  COPYRIGHT 2004 THE THOMSON CORP on STN
AN    1989-177917 [24]    WPIX
DNC   C1989-078636
TI    Regulating gene expression in eucaryotic cell with procaryotic peptide -
      acting as activator or repressor by binding to specific DNA sequences.
DC    B04 D16
IN    BRENT, R; PTASHNE, M S
PA    (HARD) HARVARD COLLEGE
```

CYC 1
PI US 4833080 A 19890523 (198924)* 11
ADT US 4833080 A US 1985-808166 19851212
PRAI US 1985-808166 19851212
IC C12N007-00; C12N015-00; C12N021-00; **C12P019-34**
AB US 4833080 A UPAB: 19930923
Expression of a gene in a eucaryotic cell is regulated by providing, in the cell, a peptide (I), derived from (or similar to) a peptide of a procaryotic cell able to bind to DNA upstream from, or within, the gene. Sufficient (I) is used to bind to the gene to control its expression.
Also new are (1) a hybrid gene consisting of DNA encoding for a DNA-binding procaryotic peptide and DNA for a gene-activating eucaryotic peptide (which enhances transcription of adjacent DNA) and (2) eucaryotic cells containing (I).
Pref. (I) is the product of the lexA, lacI, trpR or lambda cI repressor genes, or a fusion peptide derived from such genes and Eal4 (of yeast). The (I)-encoding gene can be present in a plasmid or integrated into the chromoso me.
USE/ADVANTAGE - This method allows eucaryotic gene products to be regulated specifically for production of active protein, without interference with cell growth until expression is started.
0/5
FS CPI
FA AB
MC CPI: B04-B02B2; B04-B04A1; B04-C01; D05-C11; D05-H05; D05-H12

L113 ANSWER 14 OF 16 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 1986-325559 [49] WPIX
CR 1986-087889 [13]
DNC C1986-140958
TI Polymeric support or substrate for peptide synthesis - comprising benzo-sulphonated polystyrene for increased reactivity.
DC A96 B04
IN CARPINO, L A A; **COHEN, B**
PA (RESE) RESEARCH CORP
CYC 1
PI US 4623484 A 19861118 (198649)* 5
ADT US 4623484 A US 1985-805483 19851205
PRAI US 1984-614344 19840524; US 1985-805483 19851205
IC **C07K001-04; C07K007-44**
AB US 4623484 A UPAB: 19930922
In a process for producing peptides by reacting a protected amino acid with an activated polymeric support or substrate, the improvement comprises using as the support or substrate cpds. of formula (I) (Z=polystyrene or a copolymer comprising styrene and a divinyl benzene comonomer; Y=NO2, acyl, carboxyl, formyl, CN, carbalkoxy, aryl, sulphone, alkyl sulphone, carboxyamide or halogen; R=OH, aryloxy, alkoxy, halogen, formyloxy, acyloxy, CN, amino, acylamino, alkylamino, carboxyamine, thiol, alkylthio, arylthio, aralkylthio or acylthio). Pref. (I) is 3-nitro-4-hydroxy benzosulphonated polystyrene (Ia).
USE/ADVANTAGE - Peptide bond formation between amino acids or peptides having a free amino function and another amino acid in the form of a polymeric active ester of (I) may be accomplished in minutes rather than hours with the approp. active esters of 4-hydroxy-3-nitrobenzylated polystyrene. The active esters of (I) are insensitive to moisture and alcohols in neutral solution The high physical stability of the polymeric reagents allows them to be used repeatedly and the reagents are regenerated without difficulty.
0/0
FS CPI
FA AB
MC CPI: A10-E12A; A12-W11L; B04-C03

L113 ANSWER 15 OF 16 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 1986-120528 [19] WPIX
DNN N1993-116181 DNC C1993-067714
TI Magnetically responsive reagent carrier - useful for carrying antibodies, enzymes or hapten(s), e.g. in immunoassays.
DC A14 A89 B04 D16 J04 S03
IN **COHEN, B**; HARGITAY, B; WONG, T K
PA (TECD) TECHNICON INSTR CORP; (MILE) MILES INC
CYC 5

PI	EP 180384	A	19860507	(198619)*	EN	29	
	AU 8549029	A	19860508	(198626)			
	JP 61181967	A	19860814	(198639)			
	EP 180384	B	19910424	(199117)			
	DE 3582649	G	19910529	(199123)			
	CA 1314769	C	19930323	(199317)			G01N033-546
	US 5206159	A	19930427	(199318)		7	C12N011-08
	JP 2554250	B2	19961113	(199650)		8	G01N033-553

ADT EP 180384 A EP 1985-307513 19851017; JP 61181967 A JP 1985-244251 19851101; CA 1314769 C CA 1985-493449 19851021; US 5206159 A Cont of US 1984-667514 19841101, Cont of US 1987-53562 19870521, Cont of US 1991-676010 19910327, US 1992-934287 19920825; JP 2554250 B2 JP 1985-244251 19851101
FDT JP 2554250 B2 Previous Publ. JP 61181967
PRAI US 1984-667514 19841101
REP A3...8739; FR 2454098; No-SR.Pub; US 4115534; US 4169804; US 4297337; US 4452773
IC A61K039-00; **C07K015-12**; C08K003-22; C08L033-26; C12N011-08; G01N033-54
ICM C12N011-08; G01N033-546; G01N033-553
ICS A61K039-00; **C07K015-12**; C08K003-22; C08L033-26; C12N011-00; C12Q001-00; G01N033-53; G01N033-54; G01N033-545

AB EP 180384 A UPAB: 19941102
Stable magnetically responsive reagent carrier (I) comprises a matrix of a polymeric material (II), which is swellable in an aq medium, and a superparamagnetic substance (III) colloidally and stable dispersed within the matrix. The magnetic response is pref. greater than 20% of the magnetic response of magnetite. (III) is pref. dispersed in the polymeric matrix in sufficient quantity ot impart a specific gravity of 1.2-2.7 to (I) when hydrated. Preparation of (I) by in situ generation of (III) in the interior of a preformed (II) matrix comprises (a) incorporating by passive transport iron cpds into a water-insol swellable polymeric matrix; (b) converting the ion cpds. to iron oxides; (c) washing the polymeric matrix to remove soluble by-prods; and (d) opt. bonding a reagent onto the polymeric matrix.

USE/ADVANTAGE - (I) may be used in immunassay procedures, in mfg. processes involving enzymatic reactions or in isolation or purificn. processes utilising chemical affinity, in which antibodies, enzymes or haptens are coupled to the carrier particles. Specific uses include one-step extraction of specific antibodies from a suspension, e.g. ascites fluid, by stirring them into the suspension and then drawing them out by an inhomogeneous magnetic field, and recovery of valuable or toxic ions from suspensions containing other particulate solids. The (I) particles carry reactive sites predominantly on their surface and can be caused either to migrate or to be immobilised at will by means of an inhomogenous magnetic field. In the absence of a magnetic field, the particles are easy to disperse and to resuspend in a surrounding medium because of their very low magnetic remanence and, by virtue of their small size and low relative specific gravity, their sedimentation rate is low. The particles do not clog narrow tubes of continuous flow analysers nor do they interfere with the colorimetric response of the assay as they leave a clear supernatant.
0/0
Dwg.0/0
FS CPI EPI

FA AB
MC CPI: A04-D04A; A12-V03C2; A12-W11L; B04-B02C; B04-B04C; B04-C03B;
B05-A03A; B11-B; B11-C07; B12-K04; D04-A01P; D05-A02; D05-H09;
D05-H13; J04-B01B
EPI: S03-E14H4
ABEQ EP 180384 B UPAB: 19930922
Stable magnetically responsive reagent carrier (I) comprises a matrix of a polymeric material (II), which is swellable in an aq medium, and a superparamagnetic substance (III) colloidally and stable dispersed within the matrix. The magnetic response is pref. greater than 20% of the magnetic response of magnetite. (III) is pref. dispersed in the polymeric matrix in sufficient quantity ot impart a specific gravity of 1.2-2.7 to (I) when hydrated. Prepn. of (I) by in situ generation of (III) in the interior of a preformed (II) matrix comprises (a) incorporating by passive transport iron cpds into a water-insol swellable polymeric matrix; (b) converting the ion cpds. to iron oxides; (c) washing the polymeric matrix to remove soluble by-prods; and (d) opt. bonding a reagent onto the polymeric matrix.

USE/ADVANTAGE - (I) may be used in immunoassay procedures, in mfg. processes involving enzymatic reactions or in isolation or purificn. processes utilising chemical affinity, in which antibodies, enzymes or haptens are coupled to the carrier particles. Specific uses include one-step extn. of specific antibodies from a suspension, e.g. ascites fluid, by stirring them into the suspension and then drawing them out by an inhomogeneous magnetic field, and recovery of valuable or toxic ions from suspensions contg. other particulate solids. The (I) particles carry reactive sites predominantly on their surface and can be caused either to migrate or to be immobilised at will by means of an inhomogeneous magnetic field. In the absence of a magnetic field, the particles are easy to disperse and to resuspend in a surrounding medium because of their very low magnetic remanence and, by virtue of their small size and low relative specific gravity, their sedimentation rate is low. The particles do not clog narrow tubes of continuous flow analysers nor do they interfere with the colorimetric response of the assay as they leave a clear supernatant.
0/0

L113 ANSWER 16 OF 16 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 1983-723174 [30] WPIX
DNC C1983-071848
TI Protected amino acids and di peptide(s) - with indenyl-methoxycarbonyl protecting Gp..
DC B05
IN CARPINO, L A; **COHEN, B**
PA (RESE) RESEARCH CORP
CYC 14
PI WO 8302448 A 19830721 (198330)* EN 43
RW: AT BE CH DE FR GB LU NL SE
W: DK JP
US 4394519 A 19830719 (198331)
EP 98865 A 19840125 (198405) EN
R: BE CH DE FR GB LI LU NL
JP 58502207 W 19831222 (198406)
US 4508657 A 19850402 (198516)
US 4581167 A 19860408 (198617)
EP 98865 B 19890301 (198909) EN
R: BE CH DE FR GB LI LU NL
DE 3279468 G 19890406 (198915)
IT 1163037 B 19870408 (198925)
ADT EP 98865 A EP 1982-900467 19821223; JP 58502207 W JP 1983- 19830110
PRAI US 1982-342296 19820119; US 1983-490124 19830429;
US 1984-674111 19841123
REP 2.Jnl.Ref; SSR870107; US 2723972; US 2870057; US 3510504; US 3775466; US

3875207; US 3906031; US 4108854
IC A61K000-00; C07C069-76; C07C103-52; C07C121-60; C07C125-06; C07C133-00; C07C149-40; C07C154-00; C07D233-54; **C07K001-06; C07K005-06**
AB WO 8302448 A UPAB: 19930925
(A) Protected amino acids and dipeptides of formula (I) are new: (where R is an amino acid residue; R3 and R4 are H, alkyl, aryl or aralkyl; R5 is H, alkyl, aryl, alkanyl, aralkyl, halogen or NO2; R6 is H, fused phenyl, alkyl, aryl, alkaryl, aralkyl, halogen or NO2; Q is OH or NHCHRCOOY; Y is H, alkyl or aralkyl; where the alkyl, aryl, alkaryl or aralkyl gps. contain up to 9C). (B) Intermediates of formula (II) are also new.
Preparation of (I) comprises reacting II with H2NCHRCOQ(where X is F, Cl, Br, I, CN, SR7, SAr, N3, OAr, 1-imidazolyl, 1,2,4-triazol-1-yl, 1,2,4-triazol-4-yl, tetrazol-1-yl, succinimidooxy, phthalimidooxy or benzotriazol-1-yloxy). (II) may be prepared from the corresp. alcohols or their haloformate esters by standard methods.
(I) are useful as intermediates in polypeptide synthesis. The opt. substd. indenylmethoxycarbonyl protecting gps. are highly stable to cleavage by HBr, Cl2 and CF3COOH while being readily cleaved with non-hydrolytic alkaline reagents (e.g. amines).
FS CPI
FA AB
MC CPI: B06-D03; B06-D08; B07-D03; B07-D09; B07-D13; B08-D03; B10-A11A; B10-A11B; B10-A12C; B10-A15
ABEQ EP 98865 B UPAB: 19930925
A protected amino acid of the formula (I) wherein R is an amino acid residue; R3 and R4 are each hydrogen, alkyl, aryl or alkyl; R4 is up to three hydrogen atoms, alkyl, aryl, alkaryl, aralkyl, halogen or nitro; and R6 is up to four hydrogen atoms, fused phenyl, alkyl, aryl, alkaryl, aralkyl, halogen or nitro; the alkyl, aryl, alkaryl or alkyl group containing up to nine carbon atoms.
ABEQ US 4508657 A UPAB: 19930925
Indenyl methoxy carbonyl derivs. of formula (I) are new. R3 and R4 are H, alkyl, aryl or aralkyl. R5 is up to 3 H, alkyl, aryl, alkenyl, aralkyl, halogen or NO2. R6 is up to 4 H, fused phenyl, Br, I, CN, SR7, SAr, N3, OAr, a gp. of formula (II)-(VIII) or an alkyl, aryl, alkaryl or aralkyl gp. contg. up to 9C.
A typical cpd. is 2-chloro 1-indenyl methylchloroformate. They may be prepd. by reaction of the corresp. indenyl hydroxy methyl derivs. with a cpd. YCOX, where X and Y are Cl, Br, F, CN and when X is Cl Y may also be Alkyl, Aryl, Aryl or F.
USE - As blocking agents in peptide synthesis.

=>